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(54) Title: ANTIBODIES THAT IMMUNOSPECIFICALLY BIND TO BLyS

(57) Abstract: The present invention relates to antibodies and related molecules that immunospecifically bind to BlyS. The present invention also relates to methods and compositions for detecting or diagnosing a disease or disorder associated with aberrant BlyS expression or inappropriate function of BlyS comprising antibodies or fragments or variants thereof or related molecules that immunospecifically bind to BlyS. The present invention further relates to methods and compositions for preventing, treating or ameliorating a disease or disorder associated with aberrant BlyS expression or inappropriate BlyS function comprising administering to an animal an effective amount of one or more antibodies or fragments or variants thereof or related molecules that immunospecifically bind to BlyS.

ANTIBODIES THAT IMMUNOSPECIFICALLY BIND TO BLyS

INTRODUCTION

[0001] The present invention relates to antibodies and related molecules that immunospecifically bind to BLyS. The present invention also relates to methods and compositions for detecting, diagnosing, or prognosing a disease or disorder associated with aberrant BLyS or BLyS receptor expression or inappropriate function of BLyS or BLyS receptor, comprising antibodies or fragments or variants thereof, or related molecules, that immunospecifically bind to BLyS. The present invention further relates to methods and compositions for preventing, treating or ameliorating a disease or disorder associated with aberrant BLyS or BLyS receptor expression or inappropriate BLyS function or BLyS receptor function, comprising administering to an animal, preferably a human, an effective amount of one or more antibodies or fragments or variants thereof, or related molecules, that immunospecifically bind to BLyS.

BACKGROUND OF THE INVENTION

[0002] B lymphocyte stimulator (BLyS) is a member of the tumor necrosis factor ("TNF") superfamily that induces both *in vivo* and *in vitro* B cell proliferation and differentiation (Moore *et al.*, Science 285: 260-263 (1999)). BLyS is distinguishable from other B cell growth and differentiation factors such as IL-2, IL-4, IL-5, IL-6, IL-7, IL-13, IL-15, CD40L, or CD27L (CD70) by its monocyte-specific gene and protein expression pattern and its specific receptor distribution and biological activity on B lymphocytes. BLyS expression is not detected on natural killer ("NK") cells, T cells or B cells, but is restricted to cells of myeloid origin. BLyS expression on resting monocytes is upregulated by interferon-gamma (IFN-gamma). The gene encoding BLyS has been mapped to chromosome 13q34.

[0003] BLyS is expressed as a 285 amino acid type II membrane-bound polypeptide and a soluble 152 amino acid polypeptide (Moore *et al.*, 1999 *supra*). The membrane-bound form of BLyS has a predicted transmembrane spanning domain between amino acid residues 47 and 73. The NH_2-terminus of the soluble form of BLyS begins at Ala^{134}

of the membrane-bound form of BLyS. Soluble recombinant BLyS has been shown to induce *in vitro* proliferation of murine splenic B cells and to bind to a cell-surface receptor on these cells (Moore *et al.*, 1999 *supra*). Soluble BLyS administration to mice has been shown to result in an increase in the proportion of CD45R^{dull}, Ly6D^{bright} (also known as ThB) B cells and an increase in serum IgM and IgA levels (Moore *et al.*, 1999 *supra*). Thus, BLyS displays a B cell tropism in both its receptor distribution and biological activity.

[0004] Levels of BLyS protein have been found to be elevated in patients with autoimmune disease, including systemic lupus erythematosus (SLE), rheumatoid arthritis, and Sjögren's syndrome (Zhang et al., *The Journal of Immunology,* (2001) 166:6-10; Cheema et al., *Arthritis and Rheumatism* (2001) 44:1313-1319; and Groom et al., *Journal of Clinical Investigation* (2002) 109:59-68). Furthermore, administration of a soluble form of a BLyS receptor, TACI, has been shown to alleviate the autoimmune phenotype of NZBWF1 and MRL-*lpr/lpr* mice (Gross et al., *Nature*, (2000) 404:995-999). Thus, antibodies and related molecules that immunospecifically bind to BLyS may find medical utility in, for example, the treatment of B cell disorders associated with autoimmunity. In other embodiments, antibodies and related molecules that immunospecifically bind to BLyS may find medieal utility in for example, neoplasia or immunodeficiency syndromes.

SUMMARY OF THE INVENTION

[0005] The present invention eneompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or polypeptide fragment of BLyS. In particular, the invention encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or polypeptide fragment of human BLyS (SEQ ID NOS:3228 and/or 3229) or BLyS expressed on human monocytes; murine BLyS (SEQ ID NOS:3230 and/or 3231) or BLyS expressed on murine monocytes; rat BLyS (either the soluble forms as given in SEQ ID NOS:3232, 3233, 3234 and/or 3235 or in a membrane associated form, *e.g.*, on the surface of rat monocytes); or monkey BLyS (e.g., the monkey BLyS polypeptides of SEQ ID NOS:3236 and/or 3237, the soluble form of monkey BLyS, or BLyS expressed on

monkey monocytes), preferably human BLyS. The present invention also encompasses methods and compositions for detecting, diagnosing, or prognosing diseases or disorders associated with aberrant BLyS or BLyS receptor expression or inappropriate function of BLyS or BLyS receptor in an animal, preferably a mammal, and most preferably a human, comprising, or alternatively consisting of, use of antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to BLyS. Diseases and disorders which can be detected, diagnosed, or prognosed with the antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) of the invention include, but are not limited to, immune disorders (*e.g.*, lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (*e.g.*, asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (*e.g.*, AIDS), and proliferative disorders (*e.g.*, leukemia, carcinoma, and lymphoma). The present invention further encompasses methods and compositions for preventing, treating or ameliorating diseases or disorders associated with aberrant BLyS or BLyS receptor expression or inappropriate function of BLyS or BLyS receptor in an animal, preferably a mammal, and most preferably a human, comprising, or alternatively consisting of, administering to said animal an effective amount of one or more antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to BLyS. Diseases and disorders which can be prevented, treated or ameliorated by administering an effective amount of an antibody of the invention include, but are not limited to, immune disorders (*e.g.*, lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (*e.g.*, asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (*e.g.*, AIDS), and proliferative disorders (*e.g.*, leukemia, carcinoma, and lymphoma).

[0006] Using phage display technology, the present inventors have identified single chain antibody molecules ("scFvs") that immunospecifically bind to BLyS, including seFvs that immunospecifically bind to soluble BLyS, scFvs that immunospecifically bind the membrane-bound form of BLyS, and scFvs that immunospecifically bind to both the soluble form and the membrane-bound form of BLyS. Antibodies of the present invention are defined as able to bind the membrane bound and/or soluble forms of BLyS according

to the assays described in Examples 1 through 19. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLyS, the membrane-bound form of BLyS, and/or both the soluble form and membrane-bound form of BLyS, are also encompassed by the invention, as are nucleic acid molecules that encode these scFvs, and/or molecules.

[0007] In particular, the invention relates to scFvs comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of SEQ ID NOS: 1 – 2128, preferably SEQ ID NOS:834 - 872, 1570 - 1595, and 1886 – 1908, and most preferably SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, and 1881 - 1885, as referred to in Table 1 below. In specific embodiments, the present invention relates to scFvs that immunospecifically bind the soluble form of BLyS, said scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1563 - 1880, preferably SEQ ID NOS:1570 - 1595, and most preferably SEQ ID NOS: 1563 – 1569, as referred to in Table 1, below. In other embodiments, the present invention also relates to scFvs that immunospecifically bind the membrane-bound form of BLyS, said scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1881 - 2128, preferably SEQ ID NOS:1886 - 1908, and most preferably SEQ ID NOS: 1881 - 1885, as referred to in Table 1 below. The present invention further relates to scFvs that immunospecifically bind both the membrane-bound form and soluble form of BLyS, said scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1 - 1562, preferably SEQ ID NOS: 834 - 872, and most preferably SEQ ID NOS: 1 – 46, and 321 - 329, as referred to in Table 1 below. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLyS, the membrane-bound form of BLyS, and/or both the soluble form and membrane-bound form of BLyS, are also encompassed by the invention, as are nucleic acid molecules that encode these scFvs, and/or molecules.

[0008] The present invention provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that

immunospecifically bind to a polypeptide or polypeptide fragment of BLyS, said antibodies comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of any one of the variable heavy ("VH") domains referred to in Table 1, below, or any one of the variable light ("VL") domains referred to in Table 1. In a preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908, as referred to in Table 1 below. In another preferred embodiment, antibodies (including molecules comprising or alternatively consisting of, antibody fragments or variants thereof) of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VL domain contained SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908, as referred to in Table 1 below. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLyS, the membrane-bound form of BLyS, and/or both the soluble form and membrane-bound form of BLyS, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

[0009] The present invention also provides antibodies (including molecules eomprising or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or a polypeptide fragment of BLyS, said antibodies comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of any one of the VH domains referred to in Table 1, below, and any one of the VL domains referred to in Table 1. In a preferred embodiment, the antibodies of the invention comprise or alternatively consist of, a polypeptide having the amino acid sequence of a VH and VL domain contained in the same scFv referred to in Table 1. In another preferred embodiment, antibodies of the present invention, comprise, or alternatively consist of, a VH domain from an scFv of SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908, as disclosed in Table 1, and a VL domain from an scFv SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908, as disclosed in Table 1. In another preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, the VH and VL domain from a single scFv of SEQ

ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908, as disclosed in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLyS, the membrane-bound form of BLyS, and/or both the soluble form and membrane-bound form of BLyS, are also encompassed by the invention, as are nucleie acid molecules that encode these antibodies, and/or molecules.

[0010] The present invention also provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifieally bind to a polypeptide or a polypeptide fragment of BLyS, said antibodies comprising, or alternatively consisting of, a polypeptide having the amino acid sequenee of any one, two, three or more of the VH complementarity determining regions ("CDRs") (*i.e.*, VH CDR1, VH CDR2, or VH CDR3) referred to in Table 1 and/or any one, two, three or more of the VL CDRs (*i.e.*, VL CDR1, VL CDR2, or VL CDR3) referred to in Table 1. In one embodiment, antibodies of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VH CDR1s referred to in Table 1 and/or any one of the VL CDR1s referred to in Table 1. In another embodiment, antibodies of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VH CDR2s referred to in Table 1 and/or any one of the VL CDR2s referred to in Table 1. In a preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequenee of any one of the VH CDR3s referred to in Table 1 and/or any one of the VL CDR3s referred to in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLyS, the membrane-bound form of BLyS, and/or both the soluble form and membranc-bound form of BLyS, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

[0011] In another embodiment, antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) immunospecifically bind to a polypeptide or polypeptide fragment of BLyS, and

comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VH CDR1s referred to in Table 1, any one of the VH CDR2s referred to in Table 1, and/or any one of the VH CDR3s referred to in Table 1. In another embodiment, antibodies of the present invention comprise, or alternatively consist of, a polypeptide having the amino aeid sequence of any one of the VL CDR1s referred to in Table 1, any one of the VL CDR2s referred to in Table 1, and/or any one of the VL CDR3s referred to in Table 1. In a preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, at least one, two, three, four, five, six, or more CDRs that correspond to the same seFv referred to in Table 1, more preferably where CDR1, CDR2, and CDR3 of the VL domain correspond to the same scFv or where CDR1, CDR2, and CDR3 of the VH domain correspond to the same scFv, and most preferably where all six CDRs correspond to the same scFv referred to in Table 1. Molecules eomprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLyS, the membrane-bound form of BLyS, and/or both the soluble form and membrane-bound form of BLyS, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

[0012] The present invention also provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that: immunospeeifieally bind to the soluble form of BLyS (e.g., a polypeptide consisting of amino aeids 134 - 285 of SEQ ID NO:3228); that immunospecifically bind to the membrane-bound form of BLyS (e.g., a polypeptide consisting of amino acids 1 - 285 of SEQ ID NO:3228 or a BLyS polypeptide expressed on the surface of monocytes) and/or that immunospecifieally bind to both the soluble form and membrane-bound form of BLyS. In a preferred embodiment, antibodies of the present invention immunospecifically bind to the soluble form of BLyS and comprise, or alternatively consist of, a VH domain, VH CDR1, VH CDR2, VH CDR3, VL domain, VL CDR1, VL CDR2, and/or VL CDR3 eorresponding to one or more scFvs, that immunospecifically bind to the soluble form of BLyS. In another preferred embodiment, antibodies of the present invention immunospecifically bind to the membrane-bound form of BLyS and comprise, or alternatively consist of, a VH domain, VH CDR1, VH CDR2, VH CDR3, VL domain, VL

CDR1, VL CDR2, and/or VL CDR3 corresponding to one or more scFvs, that immunospecifically bind to the membrane-bound form of BLyS. In yet another preferred embodiment, antibodies of the present invention immunospecifically bind to the soluble form and membrane-bound form of BLyS and comprise, or alternatively consist of, a VH domain, VH CDR1, VH CDR2, VH CDR3, VL domain, VL CDR1, VL CDR2, and/or VL CDR3 corresponding to one or more scFvs, that immunospeeifically binds to the soluble form and membrane-bound form of BLyS. In another preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, a VH domain and a VL domain corresponding to the same scFv disclosed in Table 1, which antibodies immunospecifically bind to the soluble form of BLyS, the membrane-bound form of BLyS, or both the soluble form and membrane-bound form of BLyS. Nucleic aeid molecules encoding these antibodies are also encompassed by the invention. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLyS, the membrane-bound form of BLyS, and/or both the soluble form and membrane-bound form of BLyS, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

[0013] The present invention also provides antibodies (including molecules comprising or alternatively consisting of, antibody fragments or variants thereof) that immunospeeifically bind to both BLyS and APRIL (preferably to the soluble forms of each of these moleeules), said antibodies eomprising, or alternatively consisting of, a polypeptide having the amino acid sequence of any one of the VH domains referred to in Table 1, below, and any one of the VL domains referred to in Table 1. In a preferred embodiment, the antibodies of the invention comprise or alternatively consist of, a polypeptide having the amino acid sequence of a VH and VL domain contained in the same scFv referred to in Table 1. In another preferred embodiment, antibodies of the present invention that immunospecifically bind to both BLyS and APRIL, comprise, or alternatively consist of, a VH domain from an scFv of SEQ ID NOS:3240-3247 as disclosed in Table 1, and a VL domain from an scFv SEQ ID NOS:3240-3247, as disclosed in Table 1. In another preferred embodiment, antibodies of the present invention that immunospecifically bind to both BLyS and APRIL comprise, or alternatively consist

of, the VH and VL domain from a single scFv of SEQ ID NOS: SEQ ID NOS:3240-3247, as disclosed in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind both BLyS and APRIL, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

[0014] The present invention also provides antibodies (including molecules comprising or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a heterotrimeric protein comprising at least one BLyS polypeptide (preferably amino acids 134-285 of SEQ ID NO:3228), said antibodies comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of any one of the VH domains referred to in Table 1, below, and any one of the VL domains referred to in Table 1. In a preferred embodiment, the antibodies of the invention that immunospecifically bind heterotrimeric protein comprising at least one BLyS polypeptide, comprise or alternatively consist of, a polypeptide having the amino acid sequence of a VH and VL domain contained in the same scFv referred to in Table 1. In another preferred embodiment, antibodies of the present invention that immunospecifically bind heterotrimeric protein comprising at least one BLyS polypeptide, comprise, or alternatively consist of, a VH domain from an scFv of SEQ ID NOS:3240-3247 as disclosed in Table 1, and a VL domain from an scFv SEQ ID NOS:3240-3247, as disclosed in Table 1. In another preferred embodiment, antibodies of the present invention that immunospecifically bind heterotrimeric protein comprising at least one BLyS polypeptide, comprise, or alternatively consist of, the VH and VL domain from a single scFv of SEQ ID NOS:3240-3247, as disclosed in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind a heterotrimeric protein comprising at least one BLyS polypeptide, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

[0015] A VH domain of an amino acid sequence disclosed herein may be combined witha VL domain of an amino acid sequence disclosed herein, or other VL domains, to provide a VH/VL pairing representing an antigen-binding site of an antibody. Similarly, a

VL domain of an amino acid sequence disclosed herein may be combined with a VH domain of an amino acid sequence disclosed herein, or other VH domains. Further, one or more CDRs disclosed herein may be taken from a VH or VL domain and incorporated into a suitable framework as discussed *infra*.

[0016] The present invention provides antibodies (ineluding molecules comprising, or alternatively consisting of, antibody fragments or variants thereof (including derivatives)) comprising, or alternatively consisting of, of VH domains, VL domains and/or CDRs described herein, which antibodies, immunospecifically bind to BLyS (e.g., soluble BLyS and membrane-bound BLyS) and can be routinely assayed for immunospecifie binding to BLyS using methods known in the art, such as, for example, the immunoassays disclosed *infra*. Antibodies and antibody fragments or variants (including derivatives) of the invention may include, for example, one or more amino acid sequence alterations (addition, deletion, substitution and/or insertion of an amino acid residue). These alterations may be made in one or more framework regions and/or one or more CDR's. The antibodies of the invention (including antibody fragments, and variants and derivative thereof) can be routinely made by methods known in the art. Molecules comprising, or alternatively consisting of, fragments or variants of any of the VH domains, VH CDRs, VL domains, and VL CDRs whose sequences are specifically disclosed herein may be employed in accordance with the present invention. Nucleic acid molecules encoding these antibodies and molecules (including fragments, variants, and derivatives) are also encompassed by the invention.

[0017] The present invention also provides panels of antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants) wherein the panel members correspond to one, two, three, four, five, ten, fifteen, twenty, or more different antibodies of the invention (e.g., whole antibodies, Fabs, $F(ab')_2$ fragments, Fd fragments, disulfide-linked Fvs (sdFvs), antiidiotypic (anti-Id) antibodies, and scFvs). The present invention further provides mixtures of antibodies, wherein the mixture corresponds to one, two, three, four, five, ten, fifteen, twenty, or more different antibodies of the invention (e.g., whole antibodies, Fabs, $F(ab')_2$ fragments, Fd fragments, disulfide-linked Fvs (sdFvs), antiidiotypic (anti-Id) antibodies, and scFvs)). The present invention also provides for compositions comprising, or alternatively consisting of, one, two, three, four, five, ten, fifteen, twenty, or more antibodies of the present invention (including

molecules comprising, or alternatively consisting of, antibody fragments or variants thereof). A composition of the invention may comprise, or alternatively consist of, one, two, three, four, five, ten, fifteen, twenty, or more amino acid sequences of one or more antibodies or fragments or variants thereof. Alternatively, a composition of the invention may comprise, or alternatively consist of, nucleic acid molecules encoding one or more antibodies of the invention.

[0018] The present invention also provides for fusion proteins comprising an antibody (ineluding molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) of the invention, and a heterologous polypeptide (*i.e.*, a polypeptide unrelated to an antibody or antibody domain). Nucleic acid molecules encoding these fusion proteins are also encompassed by the invention. A composition of the present invention may comprise, or alternatively consist of, one, two, three, four, five, ten, fifteen, twenty or more fusion proteins of the invention. Alternatively, a composition of the invention may comprise, or alternatively consist of, nucleic acid molecules encoding one, two, three, four, five, ten, fifteen, twenty or more fusion proteins of the invention.

[0019] The present invention also provides for a nucleic acid molecule, generally isolated, encoding an antibody (including molecules such as scFvs, which comprise, or alternatively consist of, an antibody fragment or variant thereof) of the invention. The present invention also provides a host cell transformed with a nucleic acid molecule of the invention and progeny thereof. The present invention also provides a method for the production of an antibody (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof) of the invention. The present invention further provides a method of expressing an antibody (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof) of the invention from a nucleic acid molecule. These and other aspects of the invention are described in further detail below.

[0020] The present invention also encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders associated with aberrant BLyS or BLyS receptor expression or inappropriate BLyS or BLyS receptor function in an animal, preferably a mammal, and most preferably a human, comprising using antibodies (including molecules which comprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically bind to BLyS. Diseases and disorders which can

be detected, diagnosed or prognosed with the antibodies of the invention include, but are not limited to, immune disorders (*e.g.*, lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodefieiency syndrome), inflammatory disorders (*e.g.*, asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (*e.g.*, AIDS), and proliferative disorders (*e.g.*, leukemia, carcinoma, and lymphoma).

[0021] In specific embodiments, the present invention encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders associated with hypergammaglobulinemia (e.g., AIDS, autoimmune diseases, and some immunodeficiencies). In other specific embodiments, the present invention encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders associated with hypogammaglobulinemia (e.g., an immunodeficiency).

[0022] The present invention further encompasses methods and compositions for preventing, treating or ameliorating diseases or disorders assoeiated with aberrant BLyS or BLyS receptor expression or inappropriate BLyS or BLyS reeeptor function in an animal, preferably a mammal, and most preferably a human, comprising administering to said animal an effective amount of one or more antibodies (including molecules which eomprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically bind to BLyS. Diseases and disorders which can be prevented, treated or inhibited by administering an effective amount of one or more antibodies or moleeules of the invention include, but are not limited to, immune disorders (*e.g.*, lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodefieiency syndrome), inflammatory disorders (*e.g.*,-asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (*e.g.*, AIDS), and proliferative disorders (*e.g.*, leukemia, carcinoma, and lymphoma).

[0023] In specific embodiments, the present invention encompasses methods and compositions (e.g., antagonistic anti-BLyS antibodies) for preventing, treating or ameliorating diseases or disorders associated with hypergammaglobulinemia (e.g., AIDS, autoimmune diseases, and some immunodeficiency syndromes). In other specific embodiments, the present invention encompasses methods and compositions (e.g., agonistic anti-BLyS antibodies) for preventing, treating or ameliorating diseases or disorders associated with hypogammaglobulinemia (e.g., an immunodeficiency syndrome).

[0024] Autoimmune disorders, diseases, or conditions that may be detected, diagnosed, prognosed, or monitored using the antibodies of the invention include, but are not limited to, autoimmune hemolytic anemia, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura, autoimmune neutropenia, autoimmunocytopenia, hemolytic anemia, antiphospholipid syndrome, dermatitis, gluten-sensitive enteropathy, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart disease, glomerulonephritis (e.g., IgA nephropathy), Multiple Sclerosis, Neuritis, Uveitis Ophthalmia, Polyendocrinopathies, Purpura (e.g., Henloch-Scoenlein purpura), Reiter's Disease, Stiff-Man Syndrome, Autoimmune Pulmonary Inflammation, myocarditis, IgA glomerulonephritis, dense deposit disease, rheumatic heart disease, Guillain-Barre Syndrome, insulin dependent diabetes mellitis, and autoimmune inflammatory eye, autoimmune thyroiditis, hypothyroidism (i.e., Hashimoto's thyroiditis, systemic lupus erhythematosus, discoid lupus, Goodpasture's syndrome, Pemphigus, Receptor autoimmunities such as, for example, (a) Graves' Disease , (b) Myasthenia Gravis, and (c) insulin resistance, autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura, rheumatoid arthritis, schleroderma with anti-collagen antibodies, mixed connective tissue disease, polymyositis/dermatomyositis, pernicious anemia, idiopathic Addison's disease, infertility, glomerulonephritis such as primary glomerulonephritis and IgA nephropathy, bullous pemphigoid, Sjögren's syndrome, diabetes mellitus, and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis), chronic active hepatitis, primary biliary cirrhosis, other endocrine gland failure, vitiligo, vasculitis, post-MI, cardiotomy syndrome, urticaria, atopic dermatitis, asthma, inflammatory myopathies, and other inflammatory, granulomatous, degenerative, and atrophic disorders).

[0025] Immunodeficiencies that may be detected, diagnosed, prognosed, or monitored using the antibodies of the invention include, but are not limited to, severe combined immunodeficiency (SCID)-X linked, SCID-autosomal, adenosine deaminase deficiency (ADA deficiency), X-linked agammaglobulinemia (XLA), Bruton's disease, congenital agammaglobulinemia, X-linked infantile agammaglobulinemia, acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, transient hypogammaglobulinemia of infancy, unspecified hypogammaglobulinemia, agammaglobulinemia, common variable

immunodeficieney (CVID) (acquired), Wiskott-Aldrich Syndrome (WAS), X-linked immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, selective IgA deficiency, IgG subclass deficiency (with or without IgA deficiency), antibody deficieney with normal or elevated Igs, immunodeficiency with thymoma, Ig heavy chain deletions, kappa chain deficicncy, B ccll lymphoproliferative disordcr (BLPD), selective IgM immunodcficicncy, recessive agammaglobulinemia (Swiss type), reticular dysgenesis, neonatal neutropenia, severc congcnital leukopenia, thymic alymphoplasia-aplasia or dysplasia with immunodeficiency, ataxia-telangicctasia, short limbed dwarfism, X-linked lymphoproliferative syndromc (XLP), Nezelof syndrome-combined immunodeficiency with Igs, purine nucleoside phosphorylase deficieney (PNP), MHC Class II deficiency (Bare Lymphocyte Syndrome) and severc combined immunodeficiency.

DEFINITIONS

[0026] The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin moleculcs, *i.e.*, moleeules that contain an antigen binding site that immunospecifically binds an antigen. As such, the term antibody encompasses not only whole antibody molecules, but also antibody fragments as well as variants (including derivatives) of antibodies and antibody fragmcnts. Examplcs of molecules which are described by the term "antibody" in this application include, but arc not limited to: single chain Fvs (scFvs), Fab fragments, Fab' fragments, $F(ab')_2$, disulfide linked Fvs (sdFvs), Fvs, and fragments comprising or alternatively consisting of, eithcr a VL or a VH domain. The term "single chain Fv" or "scFv" as used herein refers to a polypeptide comprising a VL domain of antibody linked to a VH domain of an antibody. Antibodies that immunospecifically bind to BLyS may have cross-reactivity with other antigens. Preferably, antibodies that immunospecifically bind to BLyS do not cross-react with other antigens. Antibodies that immunospecifically bind to BLyS can be identified, for cxample, by immunoassays or other techniques known to those of skill in the art, *e.g.*, the immunoassays dcscribed in the Examples below.

[0027] Antibodies of thc invcntion includc, but are not limited to, monoclonal, multispecific, human or chimerie antibodies, singlc chain antibodies, Fab fragments, F(ab′) fragments, antiidiotypic (anti-Id) antibodics (including, *e.g.*, anti-Id antibodies to

antibodies of the invention), and epitope-binding fragments of any of the above. The immunoglobulin molecules of the invention can be of any type (*e.g.*, IgG, IgE, IgM, IgD, IgA and IgY), class (*e.g.*, IgG_1, IgG_2, IgG_3, IgG_4, IgA_1 and IgA_2) or subclass of immunoglobulin molecule.

[0028] Antibodies of the invention may also include multimeric forms of antibodies. For example, antibodies of the invention may take the form of antibody dimers, trimers, or higher-order multimers of monomeric immunoglobulin molecules. Dimers of whole immunoglobulin molecules or of $F(ab')_2$ fragments are tetravalent, whereas dimers of Fab fragments or scFv molecules are bivalent. Individual monomers withon an antibody multimer may be identical or different, i.e., they may be heteromeric or homomeric antibody multimers. For example, individual antibodies within a multimer may have the same or different binding specificities. Multimerization of antibodies may be aecomplished through natural aggregation of antibodies or through chemical or recombinant linking techniques known in the art. For example, some percentage of purified antibody preparations (e.g., purified IgG1 molecules) spontaneously form protein aggregates containing antibody homodimers, and other higher-order antibody multimers. Alternatively, antibody homodimers may be formed through chemical linkage techniques known in the art. For example, heterobifunctional crosslinking agents including, but not limited to, SMCC [succinimidyl 4-(maleimidomethyl)cyclohexane-1-carboxylate] and SATA [*N*-succinimidyl *S*-acethylthio-acetate] (available, for example, from Pierce Biotechnology, Inc. (Rockford, IL)) can be used to form antibody multimers. An exemplary protocol for the formation of antibody homodimers is given in Ghetie et al., *Proceedings of the National Academy of Sciences USA* (1997) 94:7509-7514, which is hereby incorporated by reference in its entirety. Antibody homodimers can be converted to Fab'2 homodimers through digestion with pepsin. Another way to form antibody homodimers is through the use of the autophilic T15 peptide described in Zhao and Kohler, *The Journal of Immunology* (2002) 25:396-404, which is hereby incorporated by reference in its entirety.

[0029] Alternatively, antibodies can be made to multimerize through recombinant DNA techniques. IgM and IgA naturally form antibody multimers through the interaction with the J chain polypeptide. Non-IgA or non-IgM molecules, such as IgG molecules, can be engineered to contain the J chain interaction domain of IgA or IgM, thereby conferring

the ability to form higher order multimers on the non-IgA or non-IgM molecules. (see, for example, Chintalacharuvu et al., (2001) *Clinical Immunology* 101:21-31. and Frigerio et al., (2000) *Plant Physiology* 123:1483-94., both of which are hereby incorporated by reference in their entireties.) ScFv dimers can also be formed through recombinant techniques known in the art; an example of the construction of scFv dimers is given in Goel et al., (2000) *Cancer Research* 60:6964-6971 which is hereby incorporated by reference in its entirety. Antibody multimers may be purified using any suitable method known in the art, including, but not limited to, size exclusion chromatography.

[0030] Unless otherwise defined in the specification, specific binding or immunospecifc binding by an anti-BLyS antibody means that the anti-BLyS antibody binds BLyS but does not significantly bind to (i.e., cross react with) proteins other than BLyS, such as other proteins in the same family of proteins, e.g., other TNF family ligands). An antibody that binds BLyS protein and does not cross-react with other proteins is not necessarily an antibody that does not bind said other proteins in all conditions; rather, the BLyS -specific antibody of the invention preferentially binds BLyS eompared to its ability to bind said other proteins such that it will be suitable for use in at least one type of assay or treatment, i.e., give low background levels or result in no unreasonable adverse effects in treatment. It is well known that the portion of a protein bound by an antibody is known as the epitope. An epitope may either be linear (i.e., comprised of sequential amino acids residues in a protein sequences) or conformational (i.e., comprised of one or more amino acid residues that are not contiguous in the primary structure of the protein but that are brought together by the secondary, tertiary or quaternary structure of a protein). Given that BLyS -specific antibodies bind to epitopes of BLyS, an antibody that specifically binds BLyS may or may not bind fragments of BLyS and/or variants of BLyS (e.g., proteins that are at least 90% identical to BLyS) depending on the presence or absence of the epitope bound by a given BLyS-specific antibody in the BLyS fragment or variant. Likewise, BLyS-specific antibodies of the invention may bind species orthologues of BLyS (including fragments thereof) depending on the presence or absence of the epitope recognized by the antibody in the orthologue. Additionally, BLyS-specific antibodies of the invention may bind modified forms of BLyS, for example, BLyS fusion proteins. In such a case when antibodies of the invention bind BLyS fusion proteins, the antibody must make binding contact with the BLyS moiety

of the fusion protein in order for the binding to be specific. Antibodies that specifically bind to BLyS can be identified, for example, by immunoassays or other teehniques known to those of skill in the art, *e.g.*, the immunoassays described in the Examples below.

[0031] Furthermore, in the present application eertain antibodies may be specific for either the membrane bound form of BLyS, or the soluble form of BLyS (i.e., 134-285 of SEQ ID NO:2, preferably trimers of proteins consisting of amino acids 134-285 of SEQ ID NO:2), or both. Antibodies of the present invention are defined as able to bind the membrane bound and/or soluble forms of BLyS according to the assays described in Examples 1 through 19.

[0032] Preferably, an antibody of the invention comprises, or alternatively consists of, a VH domain, VH CDR, VL domain, or VL CDR having an amino acid sequence of any one of those referred to in Table 1, or a fragment or variant thereof.

[0033] An antibody of the invention "which binds the soluble form of BLyS" is one which binds the 152 amino acid soluble form of the BLyS protein (amino acids 134- 285 of SEQ ID NO:3228). In specific embodiments of the invention, an antibody of the invention "which binds the soluble form of BLyS" does not also bind the membrane-bound or membrane-associated form of BLyS. Assays which measure binding to the soluble form of BLyS include, but are not limited to, receptor binding inhibition assay or eapture of soluble BLyS from solution as described in Examples 8 and 9.

[0034] An antibody of the invention "which binds the membrane-bound form of BLyS" is one which binds the membrane-associated (uncleaved) BLyS protein. In specific embodiments of the invention, an antibody of the invention "which binds the membrane-bound form of BLyS" does not also bind the soluble form of BLyS. Binding to HIS-tagged BLyS (as described herein) in an ELISA is an indicator that an antibody binds the membrane-bound form of BLyS, but should not be relied upon as proof of specificity for the membrane-bound form of BLyS. Assays that may be relied upon as proof of an antibody's specificity for membrane-bound BLyS, include, but are not limited to, binding to plasma membranes expressing BLyS as described in Example 2. An antibody of the invention "which binds the both the soluble form and the membrane-bound form of BLyS" is one which binds both the membrane-bound form and the soluble form of BLyS.

[0035] The term "variant" as used herein refers to a polypeptide that possesses a similar or identical function as a BLyS polypeptide, a fragment of BLyS, an anti-BLyS

antibody or antibody fragment thereof, but does not necessarily comprise a similar or identical amino acid sequence of a BLyS polypeptide, a fragment of BLyS, an anti-BLyS antibody or antibody fragment thereof, or possess a similar or identical structure of a BLyS polypeptide, a fragment of BLyS, an anti-BLyS antibody or antibody fragment thereof. A variant having a similar amino acid refers to a polypeptide that satisfies at least one of the following: (a) a polypeptide comprising, or alternatively consisting of, an amino acid sequence that is at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 99% identical to the amino acid sequence of a BLyS polypeptide, a fragment of BLyS, an anti-BLyS antibody or antibody fragment thereof (including a VH domain, VHCDR, VL domain, or VLCDR having an amino acid sequence of any one of those referred to in Table 1) described herein; (b) a polypeptide encoded by a nucleotide sequence, the complementary sequence of which hybridizes under stringent conditions to a nucleotide sequence eneoding a BLyS polypeptide (e.g., SEQ ID NO:3228), a fragment of BLyS, an anti-BLyS antibody or antibody fragment thereof (ineluding a VH domain, VHCDR, VL domain, or VLCDR having an amino acid sequence of any one of those referred to in Table 1), described herein, of at least 5 amino acid residues, at least 10 amino acid residues, at least 15 amino acid residues, at least 20 amino acid residues, at least 25 amino acid residues, at least 30 amino aeid residues, at least 40 amino acid residues, at least 50 amino acid residues, at least 60 amino residues, at least 70 amino acid residues, at least 80 amino acid residues, at least 90 amino acid residues, at least 100 amino acid residues, at least 125 amino acid residues, or at least 150 amino acid residues; and (c) a polypeptide encoded by a nucleotide sequence that is at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 99%, identical to the nucleotide sequence encoding a BLyS polypeptide, a fragment of BLyS, an anti-BLyS antibody or antibody fragment thereof (including a VH domain, VHCDR, VL domain, or VLCDR having an amino acid sequence of any one of those referred to in Table 1), described herein. A polypeptide with similar structure to a BLyS polypeptide, a fragment of BLyS, an anti-BLyS antibody or antibody fragment thereof, described herein refers to a polypeptide that has a similar secondary, tertiary or quarternary structure of a BLyS polypeptide, a fragment of BLyS, an

anti-BLyS antibody, or antibody fragment thereof, described herein. The structure of a polypeptide can determined by methods known to those skilled in the art, including but not limited to, X-ray crystallography, nuclear magnetic resonance, and crystallographic electron microscopy.

[0036] To determine the percent identity of two amino acid sequences or of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino acid or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide at the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % identity = number of identical overlapping positions/total number of positions x 100%). In one embodiment, the two sequences are the same length.

[0037] The determination of percent identity between two sequences can be accomplished using a mathematical algorithm known to those of skill in the art. An example of a mathematical algorithm for comparing two sequences is the algorithm of Karlin and Altschul *Proc. Natl. Acad. Sci. USA* 87:2264-2268(1990), modified as in Karlin and Altschul *Proc. Natl. Acad. Sci. USA* 90:5873-5877(1993). The BLASTn and BLASTx programs of Altschul, et al. *J. Mol. Biol.* 215:403-410(1990) have incorporated such an alogrithm. BLAST nucleotide searches can be performed with the BLASTn program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the invention. BLAST protein searches can be performed with the BLASTx program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to a protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al. *Nucleic Acids Res.* 25:3389-3402(1997). Alternatively, PSI-BLAST can be used to perform an iterated search which detects distant relationships between molecules (*Id.*). When utilizing BLAST, Gapped BLAST, and PSI-BLAST programs, the default parameters of the respective programs (e.g., BLASTx and BLASTn) can be used. (*See* http://www.ncbi.nlm.nih.gov.)

[0038] Another example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, CABIOS (1989). The ALIGN program (version 2.0) whieh is part of the GCG sequence alignment software package has incorporated such an alogrithm. Other algorithms for sequence analysis known in the art include ADVANCE and ADAM as described in Torellis and Robotti *Comput. Appl. Biosci., 10* :3-5(1994); and FASTA deseribed in Pearson and Lipman *Proc. Natl. Acad. Sci. 85*:2444-8(1988). Within FASTA, ktup is a control option that sets the sensitivity and speed of the search.

[0039] The term "derivative" as used herein, refers to a variant polypeptide of the invention that comprises, or alternatively consists of, an amino aeid sequence of a BLyS polypeptide, a fragment of BLyS, or an antibody of the invention that immunospecifically binds to BLyS, which has been altered by the introduction of amino acid residue substitutions, deletions or additions. The term "derivative" as used herein also refers to a BLyS polypeptide, a fragment of BLyS, an antibody that immunospeeifically binds to BLyS which has been modified, *e.g.*, by the covalent attachment of any type of molecule to the polypeptide. For example, but not by way of limitation, a BLyS polypeptide, a fragment of BLyS, or an anti-BLyS antibody, may be modified, *e.g.*, by glycosylation, aeetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/bloeking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. A derivative of a BLyS polypeptide, a fragment of BLyS, or an anti-BLyS antibody, may be modified by chemical modifications using techniques known to those of skill in the art, including, but not limited to, specific chemical cleavage, acetylation, formylation, metabolie synthesis of tunicamycin, etc. Further, a derivative of a BLyS polypeptide, a fragment of BLyS, or an anti-BLyS antibody, may contain one or more non-classical amino acids. A polypeptide derivative possesses a similar or identical function as a BLyS polypeptide, a fragment of BLyS, or an anti-BLyS antibody, described herein.

[0040] The term "epitopes" as used herein refers to portions of BLyS having antigenic or immunogenic activity in an animal, preferably a mammal. An epitope having immunogenic activity is a portion of BLyS that elicits an antibody response in an animal. An eptiope having antigenie activity is a portion of BLyS to which an antibody immunospecifically binds as determined by any method known in the art, for example, by

the immunoassays described herein. Antigenic epitopes need not necessarily be immunogenic.

[0041] The term "fragment" as used herein refers to a polypeptide comprising an amino acid sequence of at least 5 amino acid residues, at least 10 amino acid residues, at least 15 amino acid residues, at least 20 amino acid residues, at least 25 amino acid residues, at least 30 amino acid residues, at least 35 amino acid residues, at least 40 amino acid residues, at least 45 amino acid residues, at least 50 amino acid residues, at least 60 amino residues, at least 70 amino acid residues, at least 80 amino acid residues, at least 90 amino acid residues, at least 100 amino acid residues, at least 125 amino acid residues, at least 150 amino acid residues, at least 175 amino acid residues, at least 200 amino acid residues, or at least 250 amino acid residues, of the amino acid sequence of BLyS, or an anti-BLyS antibody (including molecules such as scFv's, that comprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically binds to BLyS.

[0042] The term "fusion protein" as used herein refers to a polypeptide that comprises, or alternatively consists of, an amino acid sequence of an anti-BLyS antibody of the invention and an amino acid sequence of a heterologous polypeptide (*i.e.*, a polypeptide unrelated to an antibody or antibody domain).

[0043] The term "host cell" as used herein refers to the particular subject cell transfected with a nucleic acid molecule and the progeny or potential progeny of such a cell. Progeny may not be identical to the parent cell transfected with the nucleic acid molecule due to mutations or environmental influences that may occur in succeeding generations or integration of the nucleic acid molecule into the host cell genome.

[0044] By "isolated antibody" is intended an antibody removed from its native environment. Thus, an antibody produced and/or contained within a recombinant host cell is considered isolated for purposes of the present invention.

DESCRIPTION OF THE FIGURES

[0045] Figure 1. ELISA results for three scFvs, I006E07, I008D05 and I016F04, that immunospecifically bind to U937 membranes, but not to bind to or cross-react with TNF-alpha or BSA.

[0046] Figure 2. The results for three scFvs, I016H07, I001C09 and I018D07, in a receptor inhibition assay.

[0047] Figure 3. ELISA results for two scFvs (I022D01 and I031F02) demonstrating their ability to bind to human BLyS and to cross-react with mouse BLyS, but not to bind to or cross-react with other antigens of the TNF ligand family.

[0048] Figure 4. ELISA results for three scFvs (I031F09, I050A12, and I051C04) binding to U937 plasma membranes when either BLyS or TNF-alpha is used as a competitor.

[0049] Figure 5. Kinetic analysis of scFv antibody I003C02. A dilution series of I003C02 from 3nM to 825nM is shown. Association and dissociation curves were generated using a BIAcore 2000 and BIAevaluation 3.0 software.

[0050] Figure 6. Typical titration curves for two scFv antibodies (I007F11 and I050A07) are shown in Figure 6. Unlabelled BLyS competed for binding to its receptor with an IC_{50} value of 0.8 nM. The IC_{50} values for I007F11 and I050A07 are 7.9 nM and 17.1 nM , respectively. The assay was performed in triplicate and standard error bars are shown.

[0051] Figure 7. ELISA results for three scFvs clones (I074B12, I075F12 and I075A02) that immunospecifically bind to immobilized BLyS, but not to U937 plasma membranes, TNF-alpha or BSA. As a control, a phage antibody that recognizes TNFα, is also shown in Figure 7.

[0052] Figure 8. The results for two scFvs (I025B09 and I026C04) in a receptor inhibition assay.

[0053] Figure 9. ELISA results for two scFvs clones (I067F05 and I078D02) demonstrating their ability to bind to immobilized human BLyS and to cross-react with immobilized mouse BLyS, but not to bind to or cross-react with other antigens of the TNF ligand family.

[0054] As a control, a phage antibody that recognizes TNFα, is also shown in Figure 7.

[0055] Figure 10. Kinetic analysis of scFV antibody I002A01. A dilution series of I002A01from 3nM to 1650nM is shown. Association and dissociation curves were generated using a BIAcore 2000 and BIAevaluation 3.0 software.

[0056] Figure 11. Typical titration curves for two scFvs, I0068C06 and I074B12, are shown in Figure 11. Unlabelled BLyS competed for binding to its receptor with an inhibitory constant 50 (IC_{50}) value of 0.66 nM. The IC_{50} values for I0068C06 and I074B12 are 61 nM and 13 nM , respectively. The assay was performed in triplicate and standard error bars are shown.

[0057] Figure 12. ELISA results for three clones (I079C01, I081C10 and I082A02) demonstrating their ability to bind histidine-tagged BLyS, U937 plasma membranes, but not to bind immobilized biotinylated BLyS.

[0058] Figure 13. ELISA results for three scFvs (I079B04, I079F08, and I080B01) binding to U937 plasma membranes when either histidine-tagged BLyS or biotinylated BLyS is used as a competitor.

[0059] Figure 14. An example of the dissociation section of a typical sensorgram for 8 scFvs is shown in Figure 14. An anti-TNFα antibody that does not recognize BLyS was included as a control. Of the 8 scFvs exemplified, I079F06 was identified for further study due to the relatively high numbers of RU's bound to the surface.

[0060] Figure 15. A typical example of the binding curves generated for the scFv antibody I082C03 is shown in Figure 15. The off-rate for this clone was calculated as $2x10^{-3}$ s^{-1}. The affinity of I082C03 was calculated as 20 nM, assuming 100% activity of the scFv.

[0061] Figure 16. ELISA results for three scFvs (I079B04, I079F08, and I080B01) binding to P388 plasma membranes when either histidine-tagged BLyS or biotinylated BLyS is used as a competitor.

DETAILED DESCRIPTION OF THE INVENTION

[0062] The present invention encompasses antibodies (ineluding molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to BLyS or a fragment or variant of BLyS. In particular, the invention provides antibodies such as, for example, single chain Fvs (scFvs) having an

amino acid sequence of any one of SEQ ID NOS:1 - 2128, as referred to in Table 1. In particular, the present invention encompasses antibodies that immunospecifically bind to a polypeptide, a polypeptide fragment or variant, or an epitope of human BLyS (SEQ ID NOS:3228 and/or 3229) or BLyS expressed on human monoeytes; murine BLyS (SEQ ID NOS:3230 and/or 3231) or BLyS expressed on murine monocytes; rat BLyS (either the soluble forms as given in SEQ ID NOS:3232, 3233, 3234 and/or 3235 or in a membrane associated form, *e.g.*, on the surface of rat monocytes); or monkey BLyS (e.g., the monkey BLyS polypeptides of SEQ ID NOS:3236 and/or 3237, the soluble form of monkey BLyS, or BLyS expressed on monkey monocytes) (as determined by immunoassays known in the art for assaying specific antibody-antigen binding).

[0063] The polypeptide sequence shown in SEQ ID NO:3228 was obtained by sequencing and translating the cDNA of the HNEDU15 clone which was deposited on October 22, 1996 at the American Type Culture Collection, 10801 University Boulevard, Manassas, Virginia 20110-2209, and assigned ATCC Accession No. 97768. The deposited clone is contained in the pBluescript SK(-) plasmid (Stratagene, La Jolla, CA). The ATCC deposits were made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure.

[0064] The polypeptide sequence shown in SEQ ID NO:3229 was obtained by sequencing and translating the cDNA of the HDPMC52 clone, which was deposited on December 10, 1998 at the American Type Culture Collection, and assigned ATCC Accession No. 203518. The deposited clone is contained in the pBluescript SK(-) plasmid (Stratagene, La Jolla, CA). The ATCC deposits were made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure.

[0065] The BLyS polypeptides bound by the antibodies of the invention may be in monomers or multimers (i.e., dimers, trimers, tetramers and higher multimers). Accordingly, the present invention relates to antibodies that bind monomers and multimers of the BLyS polypeptides of the invention, their preparation, and compositions (preferably, pharmaceutical compositions) containing them. In specific embodiments, the antibodies of the invention bind BLyS monomers, dimers, trimers or tetramers. In additional embodiments, the antibodies of the invention bind at least dimers, at least

trimers, or at least tetramers of BLyS.

[0066] Multimeric BLyS bound by the antibodies of the invention may be homomers or heteromers. A BLyS homomer, refers to a multimer containing only BLyS polypeptides (including BLyS fragments, variants, and fusion proteins, as described herein). These homomers may contain BLyS polypeptides having identical or different amino acid sequences. In specific embodiments, the antibodies of the invention bind a BLyS homodimer (e.g., containing two BLyS polypeptides having identical or different amino acid sequences) or a BLyS homotrimer (e.g., containing three BLyS polypeptides having identical or different amino acid sequences). In a preferred embodiment, the antibodies of the invention bind homotrimers of BLyS. In additional embodiments, the antibodies of the invention bind a homomeric BLyS multimer which is at least a homodimer, at least a homotrimer, or at least a homotetramer.

[0067] Heteromeric BLyS refers to a multimer containing heterologous polypeptides (i.e., polypeptides of a different protein) in addition to the BLyS polypeptides of the invention. In a specific embodiment, the antibodies of the invention bind a BLyS heterodimer, a heterotrimer, or a heterotetramer. In additional embodiments, the antibodies of the invention bind a heteromeric BLyS multimer which is at least a heterodimer, at least a heterotrimer, or at least a heterotetramer. In highly preferred embodiments, the antibodies of the invention bind a heterotrimer comprising both BLyS polypeptides and APRIL polypeptides (SEQ ID NO:3239; GenBank Accession No. AF046888; PCT International Publication Number WO97/33902; J. Exp. Med. 188(6):1185-1190) or fragments or variants thereof. In other highly preferred embodiments, the antibodies of the invention bind a heterotrimer comprising one BLyS polypeptide (including fragments or variants) and two APRIL polypeptides (including fragments or variants). In still other highly preferred embodiments, the antibodies of the invention bind a heterotrimer comprising two BLyS polypeptides (including fragments or variants) and one APRIL polypeptide (including fragments or variants). In a further nonexclusive embodiment, the heteromers bound by the antibodies of the invention contain CD40 ligand polypeptide sequence(s), or biologically active fragment(s) or variant(s) thereof.

[0068] In particularly preferred embodiments, the antibodies of the invention bind homomeric, especially homotrimeric, BLyS polypeptides, wherein the individual protein

components of the multimers consist of the mature form of BLyS (e.g., amino acids residues 134-285 of SEQ ID NO:3228, or amino acids residues 134-266 of SEQ ID NO:3229) or fragments or variants thereof. In other specific embodiments, antibodies of the invention bind heteromeric, especially heterotrimeric, BLyS polypeptides such as a heterotrimer containing two BLyS polypeptides and one APRIL polypeptide or a heterotrimer containing one BLyS polypeptide and two APRIL polypeptides, and wherein the individual protein components of the BLyS heteromer consist of the mature extracellular soluble portion of either BLyS (e.g., amino acids residues 134-285 of SEQ ID NO:3228, or amino acids residues 134-266 of SEQ ID NO:3229) or fragments or variants thereof, or the mature extracellular soluble portion APRIL (e.g., amino aeid residues 105-250 of SEQ ID NO:3239) or fragments or variants thereof.

[0069] In specific embodiments, the antibodies of the invention bind conformational epitopes of a BLyS monomeric protein. In specific embodiments, the antibodies of the invention bind eonformational epitopes of a BLyS multimeric, especially trimeric, protein. In other embodiments, antibodies of the invention bind conformational epitopes that arise from the juxtaposition of BLyS with a heterologous polypeptide, such as might be present when BLyS forms heterotrimers (e.g., with APRIL polypeptides (e.g., SEQ ID SEQ ID NO:3239)), or in fusion proteins between BLyS and a heterologous polypeptide.

[0070] In a speeific embodiment, antibodies of the invention that specifically bind heterotrimers containing at least one BLyS polypeptide and at least one APRIL polypeptide, comprise all or a portion of SEQ ID NOS: 1881 or 1884 (e.g., one or more CDR regions, a VH domain or a VL domain). In a specific embodiment, the heterotrimers containing at least one BLyS polypeptide and at least one APRIL polypeptide comprise two BLyS polypeptides and one APRIL polypeptide. In a specific embodiment, the heterotrimers containing at least one BLyS polypeptide and at least one APRIL polypeptide comprise one BLyS polypeptide and two APRIL polypeptides.

[0071] In a specific embodiment, antibodies of the invention that specifically bind heterotrimers containing at least one BLyS polypeptide and at least one APRIL polypeptide, comprise all or a portion of any one of SEQ ID NOS: 3240-3247 (e.g., one or more CDR regions, a VH domain or a VL domain). The sequences of SEQ ID NOS: 3240-3247 are presented after Table 1 just prior to the claims. In a specific embodiment, the heterotrimers containing at least one BLyS polypeptide and at least one APRIL

polypeptide comprise two BLyS polypeptides and one APRIL polypeptide. In a speeific embodiment, the heterotrimers containing at least one BLyS polypeptide and at least one APRIL polypeptide comprise one BLyS polypeptide and two APRIL polypeptides.

[0072] BLyS multimers bound by the antibodies of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked, by for example, liposome formation. Thus, in one embodiment, BLyS multimers, such as, for example, homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, BLyS heteromultimers, such as, for example, BLyS heterotrimers or BLyS heterotetramers, are formed when polypeptides of the invention contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, BLyS multimers are formed by covalent associations with and/or between the BLyS polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the polypeptide sequence (e.g., that recited in SEQ ID NO:3228 or SEQ ID NO:3229). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a BLyS fusion protein. In one example, covalent associations are between the heterologous sequence contained in a fusion protein (see, e.g., US Patent Number 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in a BLyS-Fc fusion protein. In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from another TNF family ligand/receptor member that is capable of forming covalently associated multimers, such as for example, oseteoprotegerin (see, e.g., International Publication No. WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from CD40L, or a soluble fragment thereof. In another embodiment, two or BLyS polypeptides are joined through synthetic linkers (e.g., peptide, carbohydrate or soluble polymer linkers).

Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple BLyS polypeptides separated by peptide linkers may be produced using conventional recombinant DNA technology.

[0073] In one embodiment, antibodies of the invention immunospecifically bind a BLyS polypeptide having the amino acid sequence of SEQ ID NO:3228 or as encoded by the cDNA clone contained in ATCC No. 97768, or a polypeptide comprising a portion (i.e., a fragment) of the above polypeptides. In another embodiment, the invention provides an antibody that binds an isolated BLyS polypeptide having the amino acid sequence of SEQ ID NO:3229 or the amino acid sequence encoded by the cDNA clone contained in ATCC No. 203518, or an antibody that binds polypeptide comprising a portion (i.e, fragment) of the above polypeptides.

[0074] Antibodies of the invention that bind BLyS polypeptides may bind them in as isolated polypeptides, in their naturally occurring state and/or their native conformation. By "isolated polypeptide" is intended a polypeptide removed from its native environment. Thus, a polypeptide produced by and/or contained within a recombinant host cell is considered isolated for purposes of the present invention. Also intended as an "isolated polypeptide" are polypeptides that have been purified, partially or substantially, from a recombinant host cell. Thus, antibodies of the present invention may bind recombinantly produced BLyS polypeptides.

[0075] Antibodies of the present invention may also bind BLyS expressed on the surface of a cell, wherein said BLyS polypeptide is encoded by a polynucleotide encoding amino acids 1 to 285 of SEQ ID NO:2 operably associated with a regulatory sequence that controls expression of said polynucleotide. In certain embodiments, said BLyS polypeptide expressed on the surface of a cell is a recombinant BLyS polypeptide. In other embodiments, said BLyS polypeptide expressed on the surface of the cell is a naturally occurring BLyS polypeptide. As a non-limiting example, an antibody of the invention may bind a BLyS expressed on the surface of the cell wherein Lys-132 and/or Arg-133 of the BLyS sequence shown in SEQ ID NO:3228 is mutated to another amino acid residue, or deleted altogether, thereby preventing or diminishing release of the soluble form of BLyS from cells expressing BLyS.

[0076] Antibodies of the present invention may also bind BLyS secreted by a cell, wherein said BLyS polypeptide is encoded by a polynucleotide encoding amino acids 1 to

285 of SEQ ID NO:2 operably associated with a regulatory sequence that controls expression of said polynucleotide. In certain embodiments, said BLyS polypeptide secreted by a cell is a recombinant BLyS polypeptide. In other embodiments, said BLyS polypeptide secreted by a cell is a naturally occurring BLyS polypeptide.

[0077] Antibodies of the present invention immunospecifically bind to polypeptides comprising or alternatively, consisting of, the amino acid sequence of SEQ ID NO:3228, encoded by the cDNA contained in the plasmid having ATCC accession number 97768, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone. Antibodies of the present invention also bind to fragments of the amino acid sequence of SEQ ID NO:3228, encoded by the cDNA contained in the plasmid having ATCC accession number 97768, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone.

[0078] Additionally, antibodies of the present invention bind polypeptides comprising or alternatively, consisting of, the amino acid sequence of SEQ ID NO:3229, encoded by the cDNA contained in the plasmid having ATCC accession number 203518, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone. Antibodies of the present invention also bind to fragments of the amino acid sequence of SEQ ID NO:3229, encoded by the cDNA contained in the plasmid having ATCC accession number 203518, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone.

[0079] In addition, antibodies of the invention bind polypeptides or polypeptide fragments comprising or alternatively, consisting of, an amino acid sequence contained in SEQ ID NOS: 3230 through 3237.

[0080] In specific embodiments, the antibodies of the present invention immunospecifieally bind polypeptide fragments including polypeptides comprising or alternatively, consisting of, an amino aeid sequence contained in SEQ ID NO:3228, encoded by the cDNA contained in the deposited clone, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone. Protein fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably

as a single continuous region. Representative examples of polypeptide fragments that may be bound by the antibodies of the present invention, include, for example, fragments that comprise or alternatively, consist of from about amino acid residues: 1 to 50, 51 to 100, 101 to 150, 151 to 200, 201 to 250, and/or 251 to 285 of SEQ ID NO:3228. Moreover, polypeptide fragments can be at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 175 or 200 amino acids in length.

[0081] In specific embodiments, antibodies of the present invention bind polypeptide fragments comprising, or alternatively consisting of, amino acid residues: 1-46, 31-44, 47-72, 73-285, 73-83, 94-102, 148-152, 166-181, 185-209, 210-221, 226-237, 244-249, 253-265, and/or 277-285 of SEQ ID NO:3228. In a specific embodiment, antibodies of the invention bind an epitope comprising amino acids 165-171 of SEQ ID NO:3228. In another embodiment, the CDRs of antibodies of the invention make contacts with one or more amino acids in the the sequence of amino acids 165-171 of SEQ ID NO:3228. In another embodiment, antibodies of the invention whose CDRs make contact with one or more amino acids in the the sequence of amino acids 165-171 of SEQ ID NO:3228 disrupt BLyS- BLyS receptor interactions.

[0082] It will be recognized by one of ordinary skill in the art that mutations targeted to regions of a BLyS polypeptide of SEQ ID NO:3228 which encompass the nineteen amino acid residue insertion which is not found in the BLyS polypeptide sequence of SEQ ID NO:3229 (i.e., amino acid residues Val-142 through Lys-160 of the sequence of SEQ ID NO:3229) may affect the observed biological activities of the BLyS polypeptide. More specifically, a partial, non-limiting and non-exclusive list of such residues of the BLyS polypeptide sequence which may be targeted for mutation includes the following amino acid residues of the BLyS polypeptide sequence as shown in SEQ ID NO:3228: V-142; T-143; Q-144; D-145; C-146; L-147; Q-148; L-149; I-150; A-151; D-152; S-153; E-154; T-155; P-156; T-157; I-158; Q-159; and K-160. Thus, in specific embodiments, antibodies of the present invention that bind BLyS polypeptides which have one or more mutations in the region from V-142 through K-160 of SEQ ID NO:3228 are contemplated.

[0083] Polypeptide fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments that may be bound by antibodies of the present invention, include, for example, fragments that comprise or

alternatively, consist of from about amino acid residues: 1 to 15, 16-30, 31-46, 47-55, 56-72, 73-104, 105-163, 163-188, 186-210 and 210-284 of the amino acid sequence disclosed in SEQ ID NO:3228. Additional representative examples of polypeptide fragments that may be bound by antibodies of the present invention, include, for example, fragments that comprise or alternatively, consist of from about amino acid residues: 1 to 143, 1-150, 47-143, 47-150, 73-143, 73-150, 100-150, 140-145, 142-148, 140-150, 140-200, 140-225, and 140-266 of the amino acid sequence disclosed in SEQ ID NO:3229. Moreover, polypeptide fragments that may be bound by antibodies of the present invention, can be at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 175 or 200 amino acids in length. In this context, "about" means the particularly recited ranges and ranges larger or smaller by several, a few, 5, 4, 3, 2 or 1 amino acid residues at either or both the amino- and carboxy-termini.

[0084] Additional preferred embodiments encompass antibodies that bind polypeptide fragments comprising, or alternatively consisting of, the predicted intracellular domain of BLyS (e.g., amino acid residues 1-46 of SEQ ID NO:3228), the predicted transmembrane domain of BLyS (e.g., amino acid residues 47-72 of SEQ ID NO:3228), the predicted extracellular domain of BLyS (e.g., amino acid residues 73-285 of SEQ ID NO:3228), the mature soluble extracellular domain of BLyS (e.g., amino acids residues 134-285 of SEQ ID NO:3228), the predicted TNF conserved domain of BLyS (e.g., amino acids 191 to 284 of SEQ ID NO:3228), and a polypeptide comprising, or alternatively, consisting of the predicted intracellular domain fused to the predicted extracellular domain of BLyS (amino acid residues 1-46 fused to amino acid residues 73-285 of SEQ ID NO:3228).

[0085] Further additional preferred embodiments encompass polypeptide fragments comprising, or alternatively consisting of, the predicted intracellular domain of BLyS (amino acid residues 1-46 of SEQ ID NO:3229), the predicted transmembrane domain of BLyS (amino acid residues 47-72 of SEQ ID NO:3229), the predicted extracellular domain of BLyS (amino acid residues 73-266 of SEQ ID NO:3229), the predicted TNF conserved domain of BLyS (amino aeids 172 to 265 of SEQ ID NO:3229), and a polypeptide comprising, or alternatively, consisting of the predicted intracellular domain fused to the predicted extracellular domain of BLyS (amino acid residues 1-46 fused to amino acid residues 73-266 of SEQ ID NO:3229).

[0086] Certain additional embodiments of the invention encompass antibodies that

bind polypeptide fragments comprising, or alternatively consisting of, the predicted beta-pleated sheet regions of the BLyS polypeptides of SEQ ID NO:3228 and SEQ ID NO:3229. These polypeptide fragments comprising the beta-pleated sheets of BLyS comprise, or alternatively consist of, amino acid residues Gln-144 to Ala-151, Phe-172 to Lys-173, Ala-177 to Glu-179, Asn-183 to Ile-185, Gly-191 to Lys-204, His-210 to Val-219, Leu-226 to Pro-237, Asn-242 to Ala-251, Gly-256 to Ile-263 and/or Val-276 to Leu-284 of SEQ ID NO:3228. In another, nonexclusive embodiment, these polypeptide fragments comprising the beta-pleated sheets of BLyS comprise, or alternatively consist of, amino acid residues Phe-153 to Lys-154, Ala-158 to Glu-160, Asn-164 to Ile-166, Gly-172 to Lys-185, His-191 to Val-200, Leu-207 to Pro-218, Asn-223 to Ala-232, Gly-237 to Ile-244 and/or Val-257 to Leu-265 of SEQ ID NO:3229.

[0087] A partial, non-limiting, and exemplary list of polypeptides that may be bound by the antibodies of the invention includes polypeptides that comprise, or alternatively consist of, combinations of amino acid sequences of the invention includes, for example, [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Val-142 to Lys-160] fused to [Gly-161 to Gln-198] fused to [Val-199 to Ala-248] fused to [Gly-249 to Leu-285] of SEQ ID NO:3228; or [Met-1 to Lys-113] fused to [Val-142 to Lys-160] fused to [Gly-161 to Gln-198] fused to [Val-199 to Ala-248] fused to [Gly-249 to Leu-285] of SEQ ID NO:3228; or [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Val-142 to Lys-160] fused to [Gly-161 to Gln-198] fused to [Gly-249 to Leu-285] of SEQ ID NO:3228. Other combinations of amino acids sequences that may be bound by the antibodies of the invention may include the polypeptide fragments in an order other than that recited above (e.g., [Leu-114 to Thr-141] fused to [Val-199 to Ala-248] fused to [Gly-249 to Leu-285] fused to [Val-142 to Lys-160] of (SEQ ID NO:3228). Other combinations of amino acids sequenees that may be bound by the antibodies of the invention may also include heterologous polypeptide fragments as described herein and/or other polypeptides or polypeptide fragments of the present invention (e.g., [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Val-142 to Lys-160] fused to [Gly-161 to Gln-198] fused to [Gly-249 to Leu-285] of SEQ ID NO:3228 fused to a FLAG tag ; or [Met-1 to Lys-113] of SEQ ID NO:3228 fused to [Leu-114 to Thr-141] of SEQ ID NO:3228 fused to [Glu-135 to Asn-165] of SEQ ID NO:39 fused to [Val-142 to Lys-160] of SEQ ID NO:3228 fused to [Gly-161 to Gln-198] of SEQ ID NO:3228 fused to [Val-199 to Ala-248] of SEQ ID

NO:3228 fused to [Gly-249 to Leu-285] of SEQ ID NO:3228).

[0088] A partial, non-limiting, and exemplary list of polypeptides that may be bound by the antibodies of the invention includes polypeptides that comprise, or alternatively consist of, combinations of amino acid sequences includes, for example, [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Gly-142 to Gln-179] fused to [Val-180 to Ala-229] fused to [Gly-230 to Leu-266] of SEQ ID NO:3229; [Met-1 to Lys-113] fused to [Gly-142 to Gln-179] fused to [Val-180 to Ala-229] fused to [Gly-230 to Leu-266] of SEQ ID NO:3229; or [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Gly-142 to Gln-179] fused to [Gly-230 to Leu-266] of SEQ ID NO:3229. Other of amino acids sequences that may be bound by the antibodies of the invention combinations may include the polypeptide fragments in an order other than that recited above (e.g., [Leu-114 to Thr-141] fused to [Val-180 to Ala-229] fused to [Gly-230 to Leu-266] fused to [Gly-142 to Gln-179] of SEQ ID NO:3229). Other combinations of amino acid sequences that may be bound by the antibodies of the invention may also include heterologous polypeptide fragments as described herein and/or other polypeptides or polypeptide fragments of the present invention (e.g., [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Gly-142 to Gln-179] fused to [Gly-230 to Leu-266] of SEQ ID NO:3229 fused to a FLAG tag (SEQ ID NO:3238) or, [Met-1 to Lys-113] of SEQ ID NO:3229 fused to [Leu-114 to Thr-141] of SEQ ID NO:3229 fused to [Glu-135 to Asn-165] of SEQ ID NO:39 fused to [Gly-142 to Gln-179] of SEQ ID NO:3229 fused to [Val-180 to Ala-229] of SEQ ID NO:3229 fused to [Gly-230 to Leu-266] of SEQ ID NO:3229.

[0089] Additional embodiments of the invention encompass antibodies that bind BLyS polypeptide fragments comprising, or alternatively consisting of, functional regions of polypeptides of the invention, such as the Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and coil-regions, Kyte-Doolittle hydrophilic regions and hydrophobic regions, Eisenberg alpha- and beta-amphipathic regions, Karplus-Schulz flexible regions, Emini surface-forming regions and Jameson-Wolf regions of high antigenic index set out in Tables 9 and 10 and as described herein. In a preferred embodiment, the polypeptide fragments bound by the antibodies of the invention are antigenic (i.e., containing four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program) of a complete (i.e., full-length) BLyS

polypeptide (e.g., SEQ ID NOS:3228 and 3229).

[0090] The data representing the structural or functional attributes of the BLyS polypeptide of SEQ ID NO:3228 (Table 9) or the BLyS polypeptide of SEQ ID NO:3229 (Table 10), as described above, was generated using the various modules and algorithms of the DNA*STAR set on default parameters. Column I represents the results of a Garnier-Robson analysis of alpha helical regions; Column II represents the results of a Chou-Fasman analysis of alpha helical regions; Column III represents the results of a Garnier Robson analysis of beta sheet regions; Column IV represents the results of a Chou-Fasman analysis of beta sheet regions; Column V represents the results of a Garnier Robson analysis of turn regions; Column VI represents the results of a Chou-Fasman analysis of turn regions; Column VII represents the results of a Garnier Robson analysis of coil regions; Column VIII represents a Kyte-Doolittle hydrophilicity plot; Column IX represents a Hopp-Woods hydrophobicity plot; Column X represents the results of an Eisenberg analysis of alpha amphipathic regions; Column XI represents the results of an Eisenberg analysis of beta amphipathic regions; Column XII represents the results of a Karplus-Schultz analysis of flexible regions; Column XIII represents the Jameson-Wolf antigenic index score; and Column XIV represents the Emini surface probability plot.

[0091] In a preferred embodiment, the data presented in columns VIII, IX, XIII, and XIV of Tables 9 and 10 can be used to determine regions of the BLyS polypeptide of SEQ ID NO:3228 (Table 9) or the BLyS polypeptide of SEQ ID NO:3229 (Table 10) which exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from the data presented in columns VIII, IX, XIII, and/or XIV by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

[0092] The above-mentioned preferred regions set out in Tables 9 and 10 include, but are not limited to, regions of the aforementioned types identified by analysis of the amino acid sequence set out in SEQ ID NO:2. As set out in Tables 9 and 10, such preferred regions include Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and turn-regions, Kyte-Doolittle hydrophilic regions, Eisenberg alpha- and beta-amphipathic regions, Karplus-Schulz flexible regions, Jameson-Wolf regions of high antigenic index and Emini surface-forming

regions. Preferably, antibodies of the present invention bind BLyS polypeptides or BLyS polypeptide fragments and variants comprising regions of BLyS that combine several structural features, such as several (e.g., 1, 2, 3 , or 4) of the same or different region features set out above and in Tables 9 and 10.

Table 9

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Met	1	A	.	.	.	.	.	.	0.73	-0.71	.	.	.	0.95	1.39
Asp	2	A	.	.	.	.	T	.	1.12	-0.66	*	.	.	1.15	1.56
Asp	3	A	.	.	.	.	T	.	1.62	-1.09	*	.	.	1.15	2.12
Ser	4	A	.	.	.	.	T	.	2.01	-1.51	.	.	.	1.15	4.19
Thr	5	A	.	.	.	.	T	.	2.40	-2.13	.	.	F	1.30	4.35
Glu	6	A	A	.	.	.	.	.	2.70	-1.73	*	*	F	0.90	4.51
Arg	7	A	A	.	.	.	.	.	2.81	-1.34	*	*	F	0.90	4.51
Glu	8	A	A	.	.	.	.	.	2.00	-1.73	*	*	F	0.90	6.12
Gln	9	A	A	.	.	.	.	.	1.99	-1.53	*	*	F	0.90	2.91
Ser	10	A	.	.	B	.	.	.	2.00	-1.04	*	*	F	0.90	2.15
Arg	11	A	.	.	B	.	.	.	1.33	-0.66	*	*	F	0.90	1.66
Leu	12	A	.	.	B	.	.	.	0.41	-0.09	*	*	F	0.45	0.51
Thr	13	A	.	.	B	.	.	.	0.46	0.20	*	*	F	-0.15	0.32
Ser	14	A	A	.	.	.	.	.	0.50	-0.19	*	*	.	0.30	0.32
Cys	15	A	A	.	.	.	.	.	0.91	-0.19	*	*	.	0.30	0.78
Leu	16	A	A	.	.	.	.	.	0.80	-0.87	*	*	F	0.90	1.06
Lys	17	A	A	.	.	.	.	.	1.61	-1.36	.	*	F	0.90	1.37
Lys	18	A	A	.	.	.	.	.	1.32	-1.74	.	*	F	0.90	4.44
Arg	19	A	A	.	.	.	.	.	1.67	-1.70	.	*	F	0.90	5.33
Glu	20	A	A	.	.	.	.	.	1.52	-2.39	.	*	F	0.90	5.33
Glu	21	A	A	.	.	.	.	.	2.38	-1.70	.	*	F	0.90	2.20
Met	22	A	A	.	.	.	.	.	2.33	-1.70	.	*	F	0.90	2.24
Lys	23	A	A	.	.	.	.	.	1.62	-1.70	*	*	F	0.90	2.24
Leu	24	A	A	.	.	.	.	.	0.66	-1.13	*	*	F	0.75	0.69
Lys	25	A	A	.	.	.	.	.	0.36	-0.49	.	*	F	0.45	0.52
Glu	26	A	A	.	B	.	.	.	-0.53	-0.71	*	*	.	0.60	0.35
Cys	27	A	A	.	B	.	.	.	-0.74	-0.03	*	*	.	0.30	0.30
Val	28	A	A	.	B	.	.	.	-1.00	-0.03	*	*	.	0.30	0.12
Ser	29	A	A	.	B	.	.	.	-0.08	0.40	*	*	.	-0.30	0.11
Ile	30	A	.	.	B	.	.	.	-0.08	0.40	*	*	.	-0.30	0.40
Leu	31	A	.	.	B	.	.	.	-0.08	-0.17	*	.	.	0.45	1.08
Pro	32	.	.	.	B	.	.	C	0.29	-0.81	*	.	F	1.10	1.39
Arg	33	.	.	.	.	T	.	.	0.93	-0.81	.	*	F	1.50	2.66
Lys	34	.	.	.	.	T	.	.	0.93	-1.07	.	.	F	1.84	4.98
Glu	35	.	.	.	.	.	.	C	0.97	-1.37	*	*	F	1.98	4.32
Ser	36	.	.	.	.	.	T	C	1.89	-1.16	*	*	F	2.52	1.64
Pro	37	.	.	.	.	.	T	C	1.80	-1.16	*	*	F	2.86	1.60
Ser	38	.	.	.	.	T	T	.	1.39	-0.77	*	.	F	3.40	1.24
Val	39	A	.	.	.	.	T	.	1.39	-0.39	.	*	F	2.36	1.24
Arg	40	A	.	.	.	.	.	.	1.39	-0.77	*	*	F	2.46	1.60
Ser	41	A	.	.	.	.	.	.	1.34	-1.20	*	*	F	2.46	2.00
Ser	42	.	.	.	.	T	T	.	1.60	-1.16	.	*	F	3.06	2.67
Lys	43	.	.	.	.	T	T	.	1.09	-1.80	.	*	F	3.06	2.72
Asp	44	.	.	.	.	T	T	.	1.13	-1.11	*	*	F	3.40	1.67
Gly	45	A	.	.	.	.	T	.	0.43	-0.81	*	*	F	2.66	1.03
Lys	46	A	A	.	.	.	.	.	0.14	-0.70	.	.	F	1.77	0.52
Leu	47	A	A	.	.	.	.	.	0.13	-0.20	*	.	.	0.98	0.31
Leu	48	A	A	.	.	.	.	.	-0.72	0.29	*	.	.	0.04	0.46
Ala	49	A	A	.	.	.	.	.	-1.53	0.54	.	*	.	-0.60	0.19
Ala	50	A	A	.	.	.	.	.	-2.00	1.23	.	.	.	-0.60	0.19

Table 9 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Thr	51	A	A	.	.	.	.	.	-2.63	1.23	.	.	.	-0.60	0.19
Leu	52	A	A	.	.	.	.	.	-2.63	1.04	.	.	.	-0.60	0.19
Leu	53	A	A	.	.	.	.	.	-2.63	1.23	.	.	.	-0.60	0.15
Leu	54	A	A	.	.	.	.	.	-2.34	1.41	.	.	.	-0.60	0.09
Ala	55	A	A	.	.	.	.	.	-2.42	1.31	.	.	.	-0.60	0.14
Leu	56	A	A	.	.	.	.	.	-2.78	1.20	.	.	.	-0.60	0.09
Leu	57	A	.	.	.	.	T	.	-2.78	1.09	.	.	.	-0.20	0.06
Ser	58	A	.	.	.	.	T	.	-2.28	1.09	.	.	.	-0.20	0.05
Cys	59	A	.	.	.	.	T	.	-2.32	1.07	.	.	.	-0.20	0.09
Cys	60	A	.	.	.	.	T	.	-2.59	1.03	.	.	.	-0.20	0.08
Leu	61	.	.	B	B	.	.	.	-2.08	0.99	.	.	.	-0.60	0.04
Thr	62	.	.	B	B	.	.	.	-1.97	0.99	.	.	.	-0.60	0.11
Val	63	.	.	B	B	.	.	.	-1.91	1.20	.	.	.	-0.60	0.17
Val	64	.	.	B	B	.	.	.	-1.24	1.39	.	.	.	-0.60	0.33
Ser	65	.	.	B	B	.	.	.	-1.43	1.10	.	.	.	-0.60	0.40
Phe	66	A	.	.	B	.	.	.	-1.21	1.26	.	.	.	-0.60	0.40
Tyr	67	A	.	.	B	.	.	.	-1.49	1.11	.	.	.	-0.60	0.54
Gln	68	A	.	.	B	.	.	.	-1.44	0.97	.	.	.	-0.60	0.41
Val	69	A	.	.	B	.	.	.	-0.59	1.27	.	.	.	-0.60	0.39
Ala	70	A	.	.	B	.	.	.	-0.63	0.89	.	.	.	-0.60	0.43
Ala	71	A	.	.	B	.	.	.	0.07	0.56	.	*	.	-0.60	0.25
Leu	72	A	.	.	.	.	T	.	-0.50	0.16	.	*	.	0.10	0.55
Gln	73	A	.	.	.	.	T	.	-1.09	0.20	.	.	F	0.25	0.45
Gly	74	A	.	.	.	.	T	.	-0.53	0.20	.	.	F	0.25	0.45
Asp	75	A	.	.	.	.	T	.	-0.76	0.09	.	*	F	0.25	0.73
Leu	76	A	A	.	.	.	.	.	-0.06	0.09	.	*	F	-0.15	0.35
Ala	77	A	A	.	.	.	.	.	0.17	-0.31	.	*	.	0.30	0.69
Ser	78	A	A	.	.	.	.	.	0.17	-0.24	.	*	.	0.30	0.42
Leu	79	A	A	.	.	.	.	.	-0.30	-0.24	.	*	.	0.30	0.88
Arg	80	A	A	.	.	.	.	.	-0.30	-0.24	.	*	.	0.30	0.72
Ala	81	A	A	.	.	.	.	.	0.17	-0.34	.	*	.	0.30	0.93
Glu	82	A	A	.	.	.	.	.	0.72	-0.30	.	*	.	0.45	1.11
Leu	83	A	A	.	.	.	.	.	0.99	-0.49	.	*	.	0.30	0.77
Gln	84	A	A	.	.	.	.	.	1.21	0.01	.	*	.	-0.15	1.04
Gly	85	A	A	.	.	.	.	.	1.10	0.01	*	*	.	-0.30	0.61
His	86	A	A	.	.	.	.	.	1.73	0.01	*	*	.	-0.15	1.27
His	87	A	A	.	.	.	.	.	0.92	-0.67	.	*	.	0.75	1.47
Ala	88	A	A	.	.	.	.	.	1.52	-0.39	.	*	.	0.45	1.22
Glu	89	A	A	.	.	.	.	.	0.93	-0.39	.	.	.	0.45	1.39
Lys	90	A	A	.	.	.	.	.	0.93	-0.39	*	.	F	0.60	1.03
Leu	91	A	.	.	.	.	T	.	0.38	-0.46	*	.	.	0.85	1.01
Pro	92	A	.	.	.	.	T	.	0.07	-0.46	.	.	.	0.70	0.59
Ala	93	A	.	.	.	.	T	.	0.07	-0.03	.	.	.	0.70	0.29
Gly	94	A	.	.	.	.	T	.	-0.14	0.47	.	.	.	-0.20	0.36
Ala	95	A	.	.	.	.	.	.	-0.14	0.21	.	*	.	-0.10	0.36
Gly	96	A	.	.	.	.	.	.	0.08	-0.21	.	.	F	0.65	0.71
Ala	97	A	.	.	.	.	.	.	-0.06	-0.21	.	.	F	0.65	0.72
Pro	98	A	.	.	.	.	.	.	-0.28	-0.21	.	*	F	0.65	0.71
Lys	99	A	A	.	.	.	.	.	0.07	-0.03	.	.	F	0.45	0.59
Ala	100	A	A	.	.	.	.	.	0.66	-0.46	.	.	F	0.60	1.01

Table 9 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Gly	101	A	A	.	.	.	.	.	0.41	-0.96	.	.	F	0.90	1.13
Leu	102	A	A	.	.	.	.	.	0.79	-0.89	.	.	F	0.75	0.57
Glu	103	A	A	.	.	.	.	.	0.41	-0.46	*	.	F	0.45	0.88
Glu	104	A	A	.	.	.	.	.	-0.49	-0.46	*	.	F	0.45	0.89
Ala	105	A	A	.	.	.	.	.	-0.21	-0.24	.	.	.	0.30	0.81
Pro	106	A	A	.	.	.	.	.	-0.46	-0.44	.	.	.	0.30	0.67
Ala	107	A	A	.	.	.	.	.	0.01	0.06	.	.	.	-0.30	0.39
Val	108	A	A	.	.	.	.	.	-0.80	0.49	.	*	.	-0.60	0.38
Thr	109	A	A	.	.	.	.	.	-0.76	0.67	.	*	.	-0.60	0.20
Ala	110	A	A	.	.	.	.	.	-1.06	0.24	*	*	.	-0.30	0.40
Gly	111	A	A	.	.	.	.	.	-1.54	0.43	*	*	.	-0.60	0.38
Leu	112	A	A	.	.	.	.	.	-0.96	0.57	*	*	.	-0.60	0.23
Lys	113	.	A	B	.	.	.	.	-0.31	0.09	*	*	.	-0.30	0.39
Ile	114	.	A	B	.	.	.	.	-0.21	0.01	*	.	.	-0.30	0.61
Phe	115	.	A	B	.	.	.	.	-0.21	0.01	*	.	.	0.15	1.15
Glu	116	.	A	.	.	.	.	C	-0.08	-0.17	*	.	F	1.25	0.58
Pro	117	.	A	.	.	.	.	C	0.39	0.26	*	*	F	1.10	1.28
Pro	118	.	.	.	.	.	.	C	0.34	-0.00	.	.	F	2.20	1.47
Ala	119	.	.	.	.	.	T	C	0.89	-0.79	.	*	F	3.00	1.47
Pro	120	.	.	.	.	.	T	C	1.59	-0.36	.	*	F	2.25	0.94
Gly	121	.	.	.	.	T	T	.	1.29	-0.39	.	*	F	2.15	0.98
Glu	122	.	.	.	.	T	T	.	1.20	-0.43	.	.	F	2.00	1.30
Gly	123	.	.	.	.	.	.	C	1.41	-0.54	.	.	F	1.60	1.12
Asn	124	.	.	.	.	.	T	C	2.00	-0.57	.	.	F	1.50	1.97
Ser	125	.	.	.	.	.	T	C	1.91	-0.60	.	*	F	1.50	1.82
Ser	126	.	.	.	.	.	T	C	2.37	-0.21	.	*	F	1.54	2.47
Gln	127	.	.	.	.	.	T	C	2.37	-0.64	.	*	F	2.18	3.01
Asn	128	.	.	.	.	.	.	C	2.76	-0.64	.	.	F	2.32	3.61
Ser	129	.	.	.	.	.	T	C	2.87	-1.03	.	.	F	2.86	5.39
Arg	130	.	.	.	.	T	T	.	2.58	-1.41	*	.	F	3.40	6.09
Asn	131	.	.	.	.	T	T	.	2.02	-1.31	*	.	F	3.06	3.83
Lys	132	.	.	.	.	T	T	.	2.02	-1.07	*	.	F	2.72	2.12
Arg	133	.	.	.	.	T	.	.	1.68	-1.06	*	.	F	2.18	1.88
Ala	134	.	.	.	.	.	.	C	1.77	-0.63	*	.	F	1.64	1.15
Val	135	.	.	.	.	.	.	C	1.66	-0.60	*	.	F	1.49	0.89
Gln	136	.	.	.	.	.	.	C	1.66	-0.60	*	.	F	1.83	0.79
Gly	137	.	.	.	.	.	T	C	1.30	-0.60	*	.	F	2.52	1.35
Pro	138	.	.	.	.	.	T	C	0.33	-0.61	*	.	F	2.86	2.63
Glu	139	.	.	.	.	T	T	.	0.61	-0.61	*	.	F	3.40	1.13
Glu	140	A	.	.	.	.	T	.	1.47	-0.53	*	.	F	2.66	1.64
Thr	141	A	.	.	.	.	.	.	1.47	-0.56	.	.	F	2.12	1.84
Val	142	A	.	.	.	.	.	.	1.14	-0.99	.	.	F	1.78	1.77
Thr	143	A	.	.	.	.	T	.	0.54	-0.41	.	.	F	1.19	0.55
Gln	144	A	.	.	.	.	T	.	0.54	0.27	*	.	F	0.25	0.31
Asp	145	A	.	.	.	.	T	.	-0.27	0.19	*	.	F	0.25	0.73
Cys	146	A	.	.	.	.	T	.	-0.84	0.23	*	.	.	0.10	0.42
Leu	147	A	A	.	.	.	.	.	-0.58	0.43	*	.	.	-0.60	0.17
Gln	148	A	A	.	.	.	.	.	-0.27	0.53	*	.	.	-0.60	0.10
Leu	149	A	A	.	.	.	.	.	-0.57	0.53	*	*	.	-0.30	0.32
Ile	150	A	A	.	.	.	.	.	-0.57	0.34	*	.	.	0.30	0.52

Table 9 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Ala	151	.	A	.	.	.	.	C	-0.21	-0.34	.	*	.	1.40	0.52
Asp	152	.	.	.	.	T	T	.	0.39	-0.26	.	*	F	2.45	0.91
Ser	153	.	.	.	.	.	T	C	0.08	-0.51	.	.	F	3.00	2.00
Glu	154	.	.	.	.	.	T	C	-0.00	-0.71	.	.	F	2.70	2.86
Thr	155	.	.	.	.	.	T	C	0.89	-0.53	*	.	F	2.40	1.20
Pro	156	.	.	.	B	.	.	C	1.52	-0.13	*	.	F	1.56	1.55
Thr	157	.	.	.	B	T	.	.	1.18	-0.51	*	.	F	1.92	1.79
Ile	158	A	.	.	B	.	.	.	1.18	-0.09	.	.	F	1.08	1.23
Gln	159	.	.	.	.	T	T	.	0.93	-0.19	.	.	F	2.04	1.07
Lys	160	.	.	.	.	T	T	.	0.93	0.14	*	.	F	1.60	1.16
Gly	161	.	.	.	.	T	T	.	0.44	0.14	*	.	F	1.44	2.38
Ser	162	.	.	.	.	T	T	.	-0.10	0.24	*	.	F	1.28	1.19
Tyr	163	.	.	.	B	T	.	.	0.58	0.49	*	.	.	0.12	0.44
Thr	164	.	.	B	B	.	.	.	0.29	0.91	*	.	.	-0.44	0.69
Phe	165	.	.	B	B	.	.	.	-0.57	1.40	*	.	.	-0.60	0.54
Val	166	.	.	B	B	.	.	.	-1.03	1.70	.	.	.	-0.60	0.29
Pro	167	.	.	B	B	.	.	.	-1.03	1.63	.	.	.	-0.60	0.16
Trp	168	A	.	.	B	.	.	.	-1.49	1.53	.	*	.	-0.60	0.25
Leu	169	A	.	.	B	.	.	.	-1.13	1.53	*	.	.	-0.60	0.29
Leu	170	A	.	.	B	.	.	.	-0.32	0.89	*	.	.	-0.30	0.38
Ter	171	A	.	.	.	.	.	.	0.19	0.46	*	.	.	0.20	0.71
Phe	172	.	.	.	.	T	.	.	0.10	-0.03	*	.	.	1.80	0.85
Lys	173	.	.	.	.	T	T	.	-0.20	-0.33	*	.	F	2.60	1.38
Arg	174	.	.	.	.	.	T	C	-0.20	-0.51	.	.	F	3.00	1.04
Gly	175	.	.	.	.	.	T	C	0.61	-0.21	.	.	F	2.25	0.99
Ser	176	A	.	.	.	.	T	.	0.91	-1.00	*	.	F	2.05	0.86
Ala	177	A	A	.	.	.	.	.	1.66	-1.00	*	.	F	1.35	0.76
Leu	178	A	A	.	.	.	.	.	1.61	-1.00	.	.	F	1.20	1.54
Glu	179	A	A	.	.	.	.	.	1.50	-1.43	.	.	F	0.90	1.98
Glu	180	A	A	.	.	.	.	.	1.89	-1.41	*	.	F	0.90	3.16
Lys	181	A	A	.	.	.	.	.	1.30	-1.91	*	.	F	0.90	7.66
Glu	182	A	A	.	.	.	.	.	1.08	-1.91	.	.	F	0.90	3.10
Asn	183	A	A	.	.	.	.	.	1.03	-1.23	*	*	F	0.90	1.48
Lys	184	A	A	.	.	.	.	.	1.08	-0.59	*	.	F	0.75	0.55
Ile	185	A	A	.	.	.	.	.	1.08	-0.59	*	*	.	0.60	0.63
Leu	186	A	A	.	.	.	.	.	0.72	-0.59	*	*	.	0.60	0.68
Val	187	A	A	.	.	.	.	.	0.38	-0.50	.	*	.	0.30	0.49
Lys	188	A	A	.	.	.	.	.	0.13	-0.07	*	*	F	0.45	0.69
Glu	189	A	.	.	.	.	T	.	-0.61	0.00	*	*	F	0.40	1.32
Thr	190	.	.	.	.	T	T	.	-0.42	0.10	.	*	F	0.80	1.54
Gly	191	.	.	.	.	T	T	.	-0.50	0.24	*	.	F	0.65	0.67
Tyr	192	.	.	.	.	T	T	.	0.11	0.93	*	*	.	0.20	0.27
Phe	193	.	.	B	B	.	.	.	-0.28	1.69	.	.	.	-0.60	0.29
Phe	194	.	.	B	B	.	.	.	-0.28	1.63	.	*	.	-0.60	0.29
Ile	195	.	.	B	B	.	.	.	-0.82	1.60	.	.	.	-0.60	0.32
Tyr	196	.	.	B	B	.	.	.	-1.29	1.49	.	.	.	-0.60	0.28
Gly	197	.	.	.	B	T	.	.	-1.29	1.39	.	.	.	-0.20	0.26
Gln	198	.	.	.	B	T	.	.	-0.90	1.36	.	.	.	-0.20	0.59
Val	199	.	.	.	B	.	.	C	-0.20	1.16	.	.	.	-0.40	0.54
Leu	200	.	.	.	B	.	.	C	0.73	0.40	.	.	.	-0.10	0.92

Table 9 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Tyr	201	.	.	.	.	T	T	.	0.67	-0.03	.	.	.	1.25	1.06
Thr	202	.	.	.	.	T	T	.	0.77	0.06	.	.	F	0.80	2.06
Asp	203	.	.	.	.	T	T	.	0.18	0.17	.	.	F	0.80	3.91
Lys	204	A	.	.	.	.	T	.	0.43	-0.01	.	.	F	1.00	2.52
Thr	205	A	A	.	.	.	.	.	0.90	-0.16	.	.	F	0.60	1.73
Tyr	206	A	A	.	.	.	.	.	1.11	-0.21	.	.	.	0.45	1.03
Ala	207	A	A	.	.	.	.	.	0.61	0.29	.	.	.	-0.30	0.70
Met	208	A	A	.	.	.	.	.	-0.28	0.97	.	.	.	-0.60	0.40
Gly	209	A	A	.	B	.	.	.	-0.32	1.17	*	.	.	-0.60	0.18
His	210	A	A	.	B	.	.	.	0.10	0.81	*	.	.	-0.60	0.31
Leu	211	A	A	.	B	.	.	.	0.39	0.31	.	.	.	-0.30	0.61
Ile	212	A	A	.	B	.	.	.	1.02	-0.30	.	.	.	0.45	1.22
Gln	213	A	A	.	B	.	.	.	0.77	-0.73	.	*	.	0.75	1.80
Arg	214	A	A	.	B	.	.	.	1.08	-0.59	.	*	F	0.90	1.62
Lys	215	A	A	.	B	.	.	.	0.26	-0.77	*	*	F	0.90	3.14
Lys	216	A	A	.	B	.	.	.	0.37	-0.81	.	*	F	0.90	1.35
Val	217	.	A	B	B	.	.	.	0.91	-0.43	*	*	.	0.30	0.60
His	218	.	A	B	B	.	.	.	0.91	-0.00	.	*	.	0.30	0.29
Val	219	.	A	B	B	.	.	.	0.80	-0.00	*	*	.	0.30	0.25
Phe	220	.	.	B	B	.	.	.	-0.06	-0.00	*	.	.	0.30	0.57
Gly	221	A	.	.	B	.	.	.	-0.40	0.04	.	*	.	-0.30	0.35
Asp	222	A	.	.	.	.	.	.	-0.36	-0.07	*	.	.	0.50	0.63
Glu	223	A	.	.	.	.	.	.	-1.18	-0.03	*	.	.	0.50	0.60
Leu	224	A	.	.	B	.	.	.	-0.63	-0.17	.	.	.	0.30	0.45
Ser	225	A	.	.	B	.	.	.	-0.74	-0.11	.	.	.	0.30	0.39
Leu	226	A	.	.	B	.	.	.	-1.10	0.57	.	*	.	-0.60	0.18
Val	227	A	.	.	B	.	.	.	-0.99	1.36	.	*	.	-0.60	0.19
Thr	228	A	.	.	B	.	.	.	-1.66	0.67	*	*	.	-0.60	0.28
Leu	229	A	.	.	B	.	.	.	-1.73	0.86	*	.	.	-0.60	0.18
Phe	230	A	.	.	B	.	.	.	-1.43	0.86	*	.	.	-0.60	0.17
Arg	231	A	.	.	B	.	.	.	-0.62	0.61	*	.	.	-0.60	0.21
Cys	232	.	.	.	B	T	.	.	-0.37	0.53	*	.	.	-0.20	0.41
Ile	233	.	.	.	B	T	.	.	-0.27	0.46	*	.	.	-0.20	0.46
Gln	234	.	.	.	B	T	.	.	0.54	0.10	*	.	.	0.10	0.37
Asn	235	.	.	.	B	.	.	C	0.93	0.10	*	.	.	0.05	1.19
Met	236	.	.	.	B	.	.	C	0.01	0.01	*	.	F	0.20	2.44
Pro	237	.	.	.	B	.	.	C	0.47	0.01	*	.	F	0.44	1.16
Glu	238	.	.	.	.	T	.	.	1.36	0.04	*	.	F	1.08	1.12
Thr	239	.	.	.	.	.	.	C	1.36	0.04	*	.	F	1.12	1.82
Leu	240	.	.	.	.	.	.	C	1.06	-0.17	*	.	F	1.96	1.89
Pro	241	.	.	.	.	T	.	.	0.99	-0.21	.	.	F	2.40	1.46
Asn	242	.	.	.	.	T	.	.	0.96	0.36	.	.	F	1.41	0.54
Asn	243	.	.	.	.	T	T	.	0.66	0.63	.	.	F	1.22	1.03
Ser	244	.	.	.	.	T	T	.	0.38	0.33	.	.	F	1.13	0.89
Cys	245	.	.	.	.	T	T	.	0.84	0.40	.	.	.	0.74	0.56
Tyr	246	.	.	.	.	T	T	.	0.17	0.43	.	.	.	0.20	0.35
Ser	247	A	.	.	.	.	.	.	-0.42	0.71	.	.	.	-0.40	0.18
Ala	248	A	A	.	.	.	.	.	-0.38	0.83	.	.	.	-0.60	0.34
Gly	249	A	A	.	.	.	.	.	-0.89	0.26	.	.	.	-0.30	0.43
Ile	250	A	A	.	.	.	.	.	-0.22	0.19	*	.	.	-0.30	0.27

Table 9 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Ala	251	A	A	.	.	.	.	.	0.02	-0.20	*	.	.	0.30	0.46
Lys	252	A	A	.	.	.	.	.	-0.02	-0.70	.	.	.	0.60	0.80
Leu	253	A	A	.	.	.	.	.	0.57	-0.70	.	.	F	0.90	1.13
Glu	254	A	A	.	.	.	.	.	0.91	-1.39	.	.	F	0.90	1.87
Glu	255	A	A	.	.	.	.	.	0.99	-1.89	.	.	F	0.90	1.62
Gly	256	A	A	.	.	.	.	.	1.58	-1.20	.	*	F	0.90	1.62
Asp	257	A	A	.	.	.	.	.	0.72	-1.49	.	*	F	0.90	1.62
Glu	258	A	A	.	.	.	.	.	0.94	-0.80	*	*	F	0.75	0.77
Leu	259	A	A	.	.	.	.	.	0.06	-0.30	*	*	.	0.30	0.79
Gln	260	A	A	.	.	.	.	.	-0.16	-0.04	*	.	.	0.30	0.33
Leu	261	A	A	.	.	.	.	.	0.30	0.39	*	.	.	-0.30	0.30
Ala	262	A	A	.	.	.	.	.	0.30	0.39	*	.	.	-0.30	0.70
Ile	263	A	A	.	.	.	.	.	0.30	-0.30	.	*	.	0.30	0.70
Pro	264	A	.	.	.	.	T	.	0.52	-0.30	.	*	F	1.00	1.37
Arg	265	A	.	.	.	.	T	.	0.52	-0.49	.	*	F	1.00	1.37
Glu	266	A	.	.	.	.	T	.	0.44	-0.59	*	*	F	1.30	3.38
Asn	267	A	.	.	.	.	T	.	0.73	-0.59	*	*	F	1.30	1.53
Ala	268	A	.	.	.	.	.	.	0.81	-0.63	*	*	.	0.95	1.05
Gln	269	A	.	.	.	.	.	.	1.02	0.06	*	*	.	-0.10	0.50
Ile	270	A	.	.	.	.	.	.	0.57	0.06	.	*	.	0.15	0.52
Ser	271	.	.	.	.	.	.	C	0.57	0.09	.	*	.	0.60	0.51
Leu	272	.	.	.	.	.	.	C	-0.29	-0.41	.	*	F	1.60	0.49
Asp	273	.	.	.	.	T	T	.	-0.01	-0.17	.	*	F	2.25	0.52
Gly	274	.	.	.	.	T	T	.	-0.71	-0.37	.	*	F	2.50	0.56
Asp	275	.	.	.	.	T	T	.	-0.52	0.03	.	*	F	1.65	0.59
Val	276	A	.	.	.	.	T	.	-0.57	0.13	.	*	F	1.00	0.30
Thr	277	A	.	.	B	.	.	.	-0.34	0.56	.	*	.	-0.10	0.30
Phe	278	A	.	.	B	.	.	.	-1.16	0.63	.	*	.	-0.35	0.18
Phe	279	A	.	.	B	.	.	.	-0.77	1.31	.	*	.	-0.60	0.20
Gly	280	A	A	.	.	.	.	.	-1.58	0.67	.	*	.	-0.60	0.28
Ala	281	A	A	.	.	.	.	.	-1.53	0.87	.	*	.	-0.60	0.27
Leu	282	A	A	.	.	.	.	.	-1.61	0.77	*	.	.	-0.60	0.26
Lys	283	A	A	.	.	.	.	.	-1.30	0.41	*	.	.	-0.60	0.33
Leu	284	A	A	.	.	.	.	.	-0.99	0.41	.	.	.	-0.60	0.42
Leu	285	A	A	.	.	.	.	.	-1.03	0.34	*	.	.	-0.30	0.65

Table 10

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Met	1	A	.	.	.	.	.	.	0.73	-0.71	.	.	.	0.95	1.39
Asp	2	A	.	.	.	.	T	.	1.12	-0.66	*	.	.	1.15	1.56
Asp	3	A	.	.	.	.	T	.	1.62	-1.09	*	.	.	1.15	2.12
Ser	4	A	.	.	.	.	T	.	2.01	-1.51	.	.	.	1.15	4.19
Thr	5	A	.	.	.	.	T	.	2.40	-2.13	.	.	F	1.30	4.35
Glu	6	A	A	.	.	.	.	.	2.70	-1.73	*	*	F	0.90	4.51
Arg	7	A	A	.	.	.	.	.	2.81	-1.34	*	*	F	0.90	4.51
Glu	8	A	A	.	.	.	.	.	2.00	-1.73	*	*	F	0.90	6.12
Gln	9	A	A	.	.	.	.	.	1.99	-1.53	*	*	F	0.90	2.91
Ser	10	A	.	.	B	.	.	.	2.00	-1.04	*	*	F	0.90	2.15
Arg	11	A	.	.	B	.	.	.	1.33	-0.66	*	*	F	0.90	1.66
Leu	12	A	.	.	B	.	.	.	0.41	-0.09	*	*	F	0.45	0.51
Thr	13	A	.	.	B	.	.	.	0.46	0.20	*	*	F	-0.15	0.32
Ser	14	A	A	.	.	.	.	.	0.50	-0.19	*	*	.	0.30	0.32
Cys	15	A	A	.	.	.	.	.	0.91	-0.19	*	*	.	0.30	0.78
Leu	16	A	A	.	.	.	.	.	0.80	-0.87	*	*	F	0.90	1.06
Lys	17	A	A	.	.	.	.	.	1.61	-1.36	.	*	F	0.90	1.37
Lys	18	A	A	.	.	.	.	.	1.32	-1.74	.	*	F	0.90	4.44
Arg	19	A	A	.	.	.	.	.	1.67	-1.70	.	*	F	0.90	5.33
Glu	20	A	A	.	.	.	.	.	1.52	-2.39	.	*	F	0.90	5.33
Glu	21	A	A	.	.	.	.	.	2.38	-1.70	.	*	F	0.90	2.20
Met	22	A	A	.	.	.	.	.	2.33	-1.70	.	*	F	0.90	2.24
Lys	23	A	A	.	.	.	.	.	1.62	-1.70	*	*	F	0.90	2.24
Leu	24	A	A	.	.	.	.	.	0.66	-1.13	*	*	F	0.75	0.69
Lys	25	A	A	.	.	.	.	.	0.36	-0.49	.	*	F	0.45	0.52
Glu	26	A	A	.	B	.	.	.	-0.53	-0.71	*	*	.	0.60	0.35
Cys	27	A	A	.	B	.	.	.	-0.74	-0.03	*	*	.	0.30	0.30
Val	28	A	A	.	B	.	.	.	-1.00	-0.03	*	*	.	0.30	0.12
Ser	29	A	A	.	B	.	.	.	-0.08	0.40	*	*	.	-0.30	0.11
Ile	30	A	.	.	B	.	.	.	-0.08	0.40	*	*	.	-0.30	0.40
Leu	31	A	.	.	B	.	.	.	-0.08	-0.17	*	.	.	0.45	1.08
Pro	32	.	.	.	B	.	.	C	0.29	-0.81	*	.	F	1.10	1.39
Arg	33	.	.	.	.	T	.	.	0.93	-0.81	.	*	F	1.50	2.66
Lys	34	.	.	.	.	T	.	.	0.93	-1.07	.	.	F	1.84	4.98
Glu	35	.	.	.	.	.	.	C	0.97	-1.37	*	*	F	1.98	4.32
Ser	36	.	.	.	.	.	T	C	1.89	-1.16	*	*	F	2.52	1.64
Pro	37	.	.	.	.	.	T	C	1.80	-1.16	*	*	F	2.86	1.60
Ser	38	.	.	.	.	T	T	.	1.39	-0.77	*	.	F	3.40	1.24
Val	39	A	.	.	.	.	T	.	1.39	-0.39	.	*	F	2.36	1.24
Arg	40	A	.	.	.	.	.	.	1.39	-0.77	*	*	F	2.46	1.60
Ser	41	A	.	.	.	.	.	.	1.34	-1.20	*	*	F	2.46	2.00
Ser	42	.	.	.	.	T	T	.	1.60	-1.16	.	*	F	3.06	2.67
Lys	43	.	.	.	.	T	T	.	1.09	-1.80	*	*	F	3.06	2.72
Asp	44	.	.	.	.	T	T	.	1.13	-1.11	*	*	F	3.40	1.67
Gly	45	A	.	.	.	.	T	.	0.43	-0.81	*	*	F	2.66	1.03
Lys	46	A	A	.	.	.	.	.	0.14	-0.70	.	.	F	1.77	0.52
Leu	47	A	A	.	.	.	.	.	0.13	-0.20	*	.	.	0.98	0.31
Leu	48	A	A	.	.	.	.	.	-0.72	0.29	*	.	.	0.04	0.46
Ala	49	A	A	.	.	.	.	.	-1.53	0.54	.	*	.	-0.60	0.19
Ala	50	A	A	.	.	.	.	.	-2.00	1.23	.	.	.	-0.60	0.19

Table 10 (continued)

Res	Position	I	II	III	IV	V	V1	VII	VIII	IX	X	X1	XII	XIII	XIV
Thr	51	A	A	.	.	.	.	.	-2.63	1.23	.	.	.	-0.60	0.19
Leu	52	A	A	.	.	.	.	.	-2.63	1.04	.	.	.	-0.60	0.19
Leu	53	A	A	.	.	.	.	.	-2.63	1.23	.	.	.	-0.60	0.15
Leu	54	A	A	.	.	.	.	.	-2.34	1.41	.	.	.	-0.60	0.09
Ala	55	A	A	.	.	.	.	.	-2.42	1.31	.	.	.	-0.60	0.14
Leu	56	A	A	.	.	.	.	.	-2.78	1.20	.	.	.	-0.60	0.09
Leu	57	A	.	.	.	.	T	.	-2.78	1.09	.	.	.	-0.20	0.06
Ser	58	A	.	.	.	.	T	.	-2.28	1.09	.	.	.	-0.20	0.05
Cys	59	A	.	.	.	.	T	.	-2.32	1.07	.	.	.	-0.20	0.09
Cys	60	A	.	.	.	.	T	.	-2.59	1.03	.	.	.	-0.20	0.08
Leu	61	.	.	B	B	.	.	.	-2.08	0.99	.	.	.	-0.60	0.04
Thr	62	.	.	B	B	.	.	.	-1.97	0.99	.	.	.	-0.60	0.11
Val	63	.	.	B	B	.	.	.	-1.91	1.20	.	.	.	-0.60	0.17
Val	64	.	.	B	B	.	.	.	-1.24	1.39	.	.	.	-0.60	0.33
Ser	65	.	.	B	B	.	.	.	-1.43	1.10	.	.	.	-0.60	0.40
Phe	66	A	.	.	B	.	.	.	-1.21	1.26	.	.	.	-0.60	0.40
Tyr	67	A	.	.	B	.	.	.	-1.49	1.11	.	.	.	-0.60	0.54
Gln	68	A	.	.	B	.	.	.	-1.44	0.97	.	.	.	-0.60	0.41
Val	69	A	.	.	B	.	.	.	-0.59	1.27	.	.	.	-0.60	0.39
Ala	70	A	.	.	B	.	.	.	-0.63	0.89	.	.	.	-0.60	0.43
Ala	71	A	.	.	B	.	.	.	0.07	0.56	.	*	.	-0.60	0.25
Leu	72	A	.	.	.	.	T	.	-0.50	0.16	.	.	.	0.10	0.55
Gln	73	A	.	.	.	.	T	.	-1.09	0.20	.	.	F	0.25	0.45
Gly	74	A	.	.	.	.	T	.	-0.53	0.20	.	.	F	0.25	0.45
Asp	75	A	.	.	.	.	T	.	-0.76	0.09	.	*	F	0.25	0.73
Leu	76	A	A	.	.	.	.	.	-0.06	0.09	.	*	F	-0.15	0.35
Ala	77	A	A	.	.	.	.	.	0.17	-0.31	.	*	.	0.30	0.69
Ser	78	A	A	.	.	.	.	.	0.17	-0.24	.	*	.	0.30	0.42
Leu	79	A	A	.	.	.	.	.	-0.30	-0.24	.	*	.	0.30	0.88
Arg	80	A	A	.	.	.	.	.	-0.30	-0.24	.	*	.	0.30	0.72
Ala	81	A	A	.	.	.	.	.	0.17	-0.34	.	*	.	0.30	0.93
Glu	82	A	A	.	.	.	.	.	0.72	-0.30	.	*	.	0.45	1.11
Leu	83	A	A	.	.	.	.	.	0.99	-0.49	.	*	.	0.30	0.77
Gln	84	A	A	.	.	.	.	.	1.21	0.01	.	*	.	-0.15	1.04
Gly	85	A	A	.	.	.	.	.	1.10	0.01	*	*	.	-0.30	0.61
His	86	A	A	.	.	.	.	.	1.73	0.01	*	*	.	-0.15	1.27
His	87	A	A	.	.	.	.	.	0.92	-0.67	.	*	.	0.75	1.47
Ala	88	A	A	.	.	.	.	.	1.52	-0.39	.	*	.	0.45	1.22
Glu	89	A	A	.	.	.	.	.	0.93	-0.39	.	.	.	0.45	1.39
Lys	90	A	A	.	.	.	.	.	0.93	-0.39	*	.	F	0.60	1.03
Leu	91	A	.	.	.	.	T	.	0.38	-0.46	*	.	.	0.85	1.01
Pro	92	A	.	.	.	.	T	.	0.07	-0.46	.	.	.	0.70	0.59
Ala	93	A	.	.	.	.	T	.	0.07	-0.03	.	.	.	0.70	0.29
Gly	94	A	.	.	.	.	T	.	-0.14	0.47	.	.	.	-0.20	0.36
Ala	95	A	.	.	.	.	.	.	-0.14	0.21	.	*	.	-0.10	0.36
Gly	96	A	.	.	.	.	.	.	0.08	-0.21	.	.	F	0.65	0.71
Ala	97	A	.	.	.	.	.	.	-0.06	-0.21	.	.	F	0.65	0.72
Pro	98	A	.	.	.	.	.	.	-0.28	-0.21	.	*	F	0.65	0.71
Lys	99	A	A	.	.	.	.	.	0.07	-0.03	.	.	F	0.45	0.59
Ala	100	A	A	.	.	.	.	.	0.66	-0.46	.	.	F	0.60	1.01

Table 10 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	X1	XII	XIII	XIV
Gly	101	A	A	.	.	.	.	.	0.41	-0.96	.	.	F	0.90	1.13
Leu	102	A	A	.	.	.	.	.	0.79	-0.89	.	.	F	0.75	0.57
Glu	103	A	A	.	.	.	.	.	0.41	-0.46	*	.	F	0.45	0.88
Glu	104	A	A	.	.	.	.	.	-0.49	-0.46	*	.	F	0.45	0.89
Ala	105	A	A	.	.	.	.	.	-0.21	-0.24	.	.	.	0.30	0.81
Pro	106	A	A	.	.	.	.	.	-0.46	-0.44	.	.	.	0.30	0.67
Ala	107	A	A	.	.	.	.	.	0.01	0.06	.	.	.	-0.30	0.39
Val	108	A	A	.	.	.	.	.	-0.80	0.49	*	*	.	-0.60	0.38
Thr	109	A	A	.	.	.	.	.	-0.76	0.67	.	*	.	-0.60	0.20
Ala	110	A	A	.	.	.	.	.	-1.06	0.24	*	*	.	-0.30	0.40
Gly	111	A	A	.	.	.	.	.	-1.54	0.43	*	*	.	-0.60	0.38
Leu	112	A	A	.	.	.	.	.	-0.96	0.57	*	*	.	-0.60	0.23
Lys	113	.	A	B	.	.	.	.	-0.31	0.09	*	*	.	-0.30	0.39
Ile	114	.	A	B	.	.	.	.	-0.21	0.01	*	.	.	-0.30	0.61
Phe	115	.	A	B	.	.	.	.	-0.21	0.01	*	.	.	0.15	1.15
Glu	116	.	A	.	.	.	.	C	-0.08	-0.17	*	.	F	1.25	0.58
Pro	117	.	A	.	.	.	.	C	0.39	0.26	*	*	F	1.10	1.28
Pro	118	.	.	.	.	.	.	C	0.34	0.00	*	.	F	2.20	1.47
Ala	119	.	.	.	.	.	T	C	0.89	-0.79	.	*	F	3.00	1.47
Pro	120	.	.	.	.	.	T	C	1.59	-0.36	.	*	F	2.25	0.94
Gly	121	.	.	.	.	T	T	.	1.29	-0.39	.	*	F	2.15	0.98
Glu	122	.	.	.	.	T	T	.	1.20	-0.43	.	.	F	2.00	1.30
Gly	123	.	.	.	.	.	.	C	1.41	-0.54	.	.	F	1.60	1.12
Asn	124	.	.	.	.	.	T	C	2.00	-0.57	.	.	F	1.50	1.97
Ser	125	.	.	.	.	.	T	C	1.91	-0.60	.	*	F	1.50	1.82
Ser	126	.	.	.	.	.	T	C	2.37	-0.21	.	*	F	1.54	2.47
Gln	127	.	.	.	.	.	T	C	2.37	-0.64	.	*	F	2.18	3.01
Asn	128	.	.	.	.	.	.	C	2.76	-0.64	.	.	F	2.32	3.61
Ser	129	.	.	.	.	.	T	C	2.87	-1.03	.	.	F	2.86	5.39
Arg	130	.	.	.	.	T	T	.	2.58	-1.41	*	.	F	3.40	6.09
Asn	131	.	.	.	.	T	T	.	2.02	-1.31	*	.	F	3.06	3.83
Lys	132	.	.	.	.	T	T	.	2.02	-1.07	*	.	F	2.72	2.12
Arg	133	.	.	.	.	T	.	.	1.68	-1.06	*	.	F	2.18	1.88
Ala	134	.	.	.	.	.	.	C	1.77	-0.63	*	.	F	1.64	1.15
Val	135	.	.	.	.	.	.	C	1.66	-0.60	*	.	F	1.15	0.89
Gln	136	.	.	.	.	.	.	C	1.66	-0.60	*	.	F	1.49	0.79
Gly	137	.	.	.	.	.	T	C	1.30	-0.60	*	.	F	2.18	1.35
Pro	138	.	.	.	.	.	T	C	0.84	-0.61	*	.	F	2.52	2.63
Glu	139	.	.	.	.	.	T	C	1.13	-0.83	*	.	F	2.86	1.50
Glu	140	.	.	.	.	T	T	.	1.74	-0.84	.	.	F	3.40	2.03
Thr	141	.	.	.	.	T	.	.	1.43	-0.51	.	.	F	2.86	2.06
Gly	142	.	.	.	.	T	T	.	1.08	-0.46	.	.	F	2.42	1.72
Ser	143	.	.	.	.	T	T	.	0.43	0.33	.	.	F	1.33	0.86
Tyr	144	.	.	.	.	T	T	.	0.22	0.97	.	.	.	0.54	0.44
Thr	145	.	.	.	.	T	T	.	-0.07	0.91	.	.	.	0.20	0.69
Phe	146	.	.	B	B	.	.	.	-0.57	1.40	.	.	.	-0.60	0.54
Val	147	.	.	B	B	.	.	.	-1.03	1.70	.	.	.	-0.60	0.29
Pro	148	.	.	B	B	.	.	.	-1.03	1.63	.	.	.	-0.60	0.16
Trp	149	A	.	.	B	.	.	.	-1.49	1.53	.	*	.	-0.60	0.25
Leu	150	A	.	.	B	.	.	.	-1.13	1.53	*	.	.	-0.60	0.29

Table 10 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Leu	151	A	.	.	B	.	.	.	-0.32	0.89	*	.	.	-0.30	0.38
Ser	152	A	.	.	.	.	.	.	0.19	0.46	*	.	.	0.20	0.71
Phe	153	.	.	.	.	T	.	.	0.10	-0.03	*	.	.	1.80	0.85
Lys	154	.	.	.	.	T	T	.	-0.20	-0.33	*	.	F	2.60	1.38
Arg	155	.	.	.	.	.	T	C	-0.20	-0.51	.	.	F	3.00	1.04
Gly	156	.	.	.	.	.	T	C	0.61	-0.21	.	.	F	2.25	0.99
Ser	157	A	.	.	.	.	T	.	0.91	-1.00	*	.	F	2.05	0.86
Ala	158	A	A	.	.	.	.	.	1.66	-1.00	*	.	F	1.35	0.76
Leu	159	A	A	.	.	.	.	.	1.61	-1.00	.	.	F	1.20	1.54
Glu	160	A	A	.	.	.	.	.	1.50	-1.43	.	.	F	0.90	1.98
Glu	161	A	A	.	.	.	.	.	1.89	-1.41	*	.	F	0.90	3.16
Lys	162	A	A	.	.	.	.	.	1.30	-1.91	*	.	F	0.90	7.66
Glu	163	A	A	.	.	.	.	.	1.08	-1.91	.	.	F	0.90	3.10
Asn	164	A	A	.	.	.	.	.	1.03	-1.23	*	*	F	0.90	1.48
Lys	165	A	A	.	.	.	.	.	1.08	-0.59	*	.	F	0.75	0.55
Ile	166	A	A	.	.	.	.	.	1.08	-0.59	*	*	.	0.60	0.63
Leu	167	A	A	.	.	.	.	.	0.72	-0.59	*	*	.	0.76	0.68
Val	168	A	A	.	.	.	.	.	0.38	-0.50	.	*	.	0.92	0.49
Lys	169	A	A	.	.	.	.	.	0.13	-0.07	*	*	F	0.93	0.69
Glu	170	A	.	.	.	.	T	.	-0.61	0.00	*	*	F	1.64	1.32
Thr	171	.	.	.	.	T	T	.	-0.42	0.10	.	*	F	1.60	1.54
Gly	172	.	.	.	.	T	T	.	-0.50	0.24	*	.	F	1.29	0.67
Tyr	173	.	.	.	.	T	T	.	0.11	0.93	*	*	.	0.68	0.27
Phe	174	.	.	B	B	.	.	.	-0.28	1.69	.	.	.	-0.28	0.29
Phe	175	.	.	B	B	.	.	.	-0.28	1.63	.	*	.	-0.44	0.29
Ile	176	.	.	B	B	.	.	.	-0.82	1.60	.	.	.	-0.60	0.32
Tyr	177	.	.	B	B	.	.	.	-1.29	1.49	.	.	.	-0.60	0.28
Gly	178	.	.	.	B	T	.	.	-1.29	1.39	.	.	.	-0.20	0.26
Gln	179	.	.	.	B	T	.	.	-0.90	1.36	.	.	.	-0.20	0.59
Val	180	.	.	.	B	.	.	C	-0.20	1.16	.	.	.	-0.40	0.54
Leu	181	.	.	.	B	.	.	C	0.73	0.40	.	.	.	-0.10	0.92
Tyr	182	.	.	.	.	T	T	.	0.67	-0.03	.	.	.	1.25	1.06
Thr	183	.	.	.	.	T	T	.	0.77	0.06	.	.	F	0.80	2.06
Asp	184	.	.	.	.	T	T	.	0.18	0.17	.	.	F	0.80	3.91
Lys	185	A	.	.	.	.	T	.	0.43	-0.01	.	.	F	1.00	2.52
Thr	186	A	A	.	.	.	.	.	0.90	-0.16	.	.	F	0.60	1.73
Tyr	187	A	A	.	.	.	.	.	1.11	-0.21	.	.	.	0.45	1.03
Ala	188	A	A	.	.	.	.	.	0.61	0.29	.	.	.	-0.30	0.70
Met	189	A	A	.	.	.	.	.	-0.28	0.97	.	.	.	-0.60	0.40
Gly	190	A	A	.	B	.	.	.	-0.32	1.17	*	.	.	-0.60	0.18
His	191	A	A	.	B	.	.	.	0.10	0.81	*	.	.	-0.60	0.31
Leu	192	A	A	.	B	.	.	.	0.39	0.31	.	.	.	-0.30	0.61
Ile	193	A	A	.	B	.	.	.	1.02	-0.30	.	.	.	0.45	1.22
Gln	194	A	A	.	B	.	.	.	0.77	-0.73	.	*	.	0.75	1.80
Arg	195	A	A	.	B	.	.	.	1.08	-0.59	*	*	F	0.90	1.62
Lys	196	A	A	.	B	.	.	.	0.26	-0.77	*	*	F	0.90	3.14
Lys	197	A	A	.	B	.	.	.	0.37	-0.81	.	*	F	0.90	1.35
Val	198	.	A	B	B	.	.	.	0.91	-0.43	*	*	.	0.30	0.60
His	199	.	A	B	B	.	.	.	0.91	0.00	*	*	.	0.30	0.29
Val	200	.	A	B	B	.	.	.	0.80	0.00	*	*	.	0.30	0.25

Table 10 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Phe	201	.	.	B	B	.	.	.	-0.06	0.00	*	.	.	0.30	0.57
Gly	202	A	.	.	B	.	.	.	-0.40	0.04	.	*	.	-0.30	0.35
Asp	203	A	.	.	.	.	.	.	-0.36	-0.07	*	.	.	0.50	0.63
Glu	204	A	.	.	.	.	.	.	-1.18	-0.03	*	.	.	0.50	0.60
Leu	205	A	.	.	B	.	.	.	-0.63	-0.17	.	.	.	0.30	0.45
Ser	206	A	.	.	B	.	.	.	-0.74	-0.11	.	.	.	0.30	0.39
Leu	207	A	.	.	B	.	.	.	-1.10	0.57	.	*	.	-0.60	0.18
Val	208	A	.	.	B	.	.	.	-0.99	1.36	.	*	.	-0.60	0.19
Thr	209	A	.	.	B	.	.	.	-1.66	0.67	*	*	.	-0.60	0.28
Leu	210	A	.	.	B	.	.	.	-1.73	0.86	*	.	.	-0.60	0.18
Phe	211	A	.	.	B	.	.	.	-1.43	0.86	*	.	.	-0.60	0.17
Arg	212	A	.	.	B	.	.	.	-0.62	0.61	*	.	.	-0.60	0.21
Cys	213	.	.	.	B	T	.	.	-0.37	0.53	*	.	.	-0.20	0.41
Ile	214	.	.	.	B	T	.	.	-0.27	0.46	*	.	.	-0.20	0.46
Gln	215	.	.	.	B	T	.	.	0.54	0.10	*	.	.	0.10	0.37
Asn	216	.	.	.	B	.	.	C	0.93	0.10	*	.	.	0.05	1.19
Met	217	.	.	.	B	.	.	C	0.01	0.01	*	.	F	0.20	2.44
Pro	218	.	.	.	B	.	.	C	0.47	0.01	*	.	F	0.44	1.16
Glu	219	.	.	.	.	T	.	.	1.36	0.04	*	.	F	1.08	1.12
Thr	220	.	.	.	.	.	.	C	1.36	0.04	*	.	F	1.12	1.82
Leu	221	.	.	.	.	.	.	C	1.06	-0.17	*	.	F	1.96	1.89
Pro	222	.	.	.	.	T	.	.	0.99	-0.21	.	.	F	2.40	1.46
Asn	223	.	.	.	.	T	.	.	0.96	0.36	.	.	F	1.41	0.54
Asn	224	.	.	.	.	T	T	.	0.66	0.63	.	.	F	1.22	1.03
Ser	225	.	.	.	.	T	T	.	0.38	0.33	.	.	F	1.13	0.89
Cys	226	.	.	.	.	T	T	.	0.84	0.40	.	.	.	0.74	0.56
Tyr	227	.	.	.	.	T	T	.	0.17	0.43	.	.	.	0.20	0.35
Ser	228	A	.	.	.	.	.	.	-0.42	0.71	.	.	.	-0.40	0.18
Ala	229	A	A	.	.	.	.	.	-0.38	0.83	.	.	.	-0.60	0.34
Gly	230	A	A	.	.	.	.	.	-0.89	0.26	.	.	.	-0.30	0.43
Ile	231	A	A	.	.	.	.	.	-0.22	0.19	*	.	.	-0.30	0.27
Ala	232	A	A	.	.	.	.	.	0.02	-0.20	*	.	.	0.30	0.46
Lys	233	A	A	.	.	.	.	.	-0.02	-0.70	.	.	.	0.60	0.80
Leu	234	A	A	.	.	.	.	.	0.57	-0.70	.	.	F	0.90	1.13
Glu	235	A	A	.	.	.	.	.	0.91	-1.39	.	.	F	0.90	1.87
Glu	236	A	A	.	.	.	.	.	0.99	-1.89	.	.	F	0.90	1.62
Gly	237	A	A	.	.	.	.	.	1.58	-1.20	.	*	F	0.90	1.62
Asp	238	A	A	.	.	.	.	.	0.72	-1.49	.	*	F	0.90	1.62
Glu	239	A	A	.	.	.	.	.	0.94	-0.80	*	*	F	0.75	0.77
Leu	240	A	A	.	.	.	.	.	0.06	-0.30	*	*	.	0.30	0.79
Gln	241	A	A	.	.	.	.	.	-0.16	-0.04	*	.	.	0.30	0.33
Leu	242	A	A	.	.	.	.	.	0.30	0.39	*	.	.	-0.30	0.30
Ala	243	A	A	.	.	.	.	.	0.30	0.39	*	.	.	-0.30	0.70
Ile	244	A	A	.	.	.	.	.	0.30	-0.30	.	*	.	0.30	0.70
Pro	245	A	.	.	.	.	T	.	0.52	-0.30	.	*	F	1.00	1.37
Arg	246	A	.	.	.	.	T	.	0.52	-0.49	.	*	F	1.00	1.37
Glu	247	A	.	.	.	.	T	.	0.44	-0.59	*	*	F	1.30	3.38
Asn	248	A	.	.	.	.	T	.	0.73	-0.59	*	*	F	1.30	1.53
Ala	249	A	.	.	.	.	.	.	0.81	-0.63	*	*	.	0.95	1.05
Gln	250	A	.	.	.	.	.	.	1.02	0.06	*	*	.	-0.10	0.50

Table 10 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Ile	251	A	.	.	.	.	.	.	0.57	0.06	*	*	.	0.15	0.52
Ser	252	.	.	.	.	.	.	C	0.57	0.09	.	*	.	0.60	0.51
Leu	253	.	.	.	.	.	.	C	-0.29	-0.41	.	*	F	1.60	0.49
Asp	254	.	.	.	.	T	T	.	-0.01	-0.17	.	*	F	2.25	0.52
Gly	255	.	.	.	.	T	T	.	-0.71	-0.37	.	*	F	2.50	0.56
Asp	256	.	.	.	.	T	T	.	-0.52	0.03	.	*	F	1.65	0.59
Val	257	A	.	.	.	.	T	.	-0.57	0.13	.	*	F	1.00	0.30
Thr	258	A	.	.	B	.	.	.	-0.34	0.56	.	*	.	-0.10	0.30
Phe	259	A	.	.	B	.	.	.	-1.16	0.63	.	*	.	-0.35	0.18
Phe	260	A	.	.	B	.	.	.	-0.77	1.31	.	*	.	-0.60	0.20
Gly	261	A	A	.	.	.	.	.	-1.58	0.67	.	*	.	-0.60	0.28
Ala	262	A	A	.	.	.	.	.	-1.53	0.87	.	*	.	-0.60	0.27
Leu	263	A	A	.	.	.	.	.	-1.61	0.77	*	.	.	-0.60	0.26
Lys	264	A	A	.	.	.	.	.	-1.30	0.41	*	.	.	-0.60	0.33
Leu	265	A	A	.	.	.	.	.	-0.99	0.41	.	.	.	-0.60	0.42
Leu	266	A	A	.	.	.	.	.	-1.03	0.34	*	.	.	-0.30	0.65

[0093] In another embodiment, the invention provides antibodies that bind a polypeptide comprising, or alternatively consisting of, an epitope-bearing portion of a polypeptide of the invention. The epitope of this polypeptide portion may be an immunogenic or antigenic epitope of a polypeptide of the invention. An "immunogenic epitope" is defined as a part of a protein that elicits an antibody response when the whole protein is the immunogen. On the other hand, a region of a protein molecule to which an antibody can bind is defined as an "antigenic epitope." The number of immunogenic epitopes of a protein generally is less than the number of antigenic epitopes. See, for instance, Geysen *et al., Proc. Natl. Acad. Sci. USA 81*:3998- 4002 (1983).

[0094] As to the selection of polypeptides bearing an antigenic epitope (i.e., that contain a region of a protein molecule to which an antibody can bind), it is well known in that art that relatively short synthetic peptides that mimic part of a protein sequence are routinely capable of eliciting an antiserum that reacts with the partially mimicked protein. See, for instance, Sutcliffe, J. G., Shinnick, T. M., Green, N. and Learner, R. A. (1983) "Antibodies that react with predetermined sites on proteins", *Science, 219*:660-666. Peptides capable of eliciting protein-reactive sera are frequently represented in the primary sequence of a protein, can be characterized by a set of simple chemical rules, and are confined neither to immunodominant regions of intact proteins (i.e., immunogenic epitopes) nor to the amino or carboxyl terminals. Antigenic epitope-bearing peptides and polypeptides of the invention are therefore useful to raise antibodies, including monoclonal antibodies, that bind specifically to a polypeptide of the invention. See, for instance, Wilson *et al., Cell 37*:767-778 (1984) at 777.

[0095] In specific embodiments, antibodies of the present invention bind antigenic epitope-bearing peptides and polypeptides of BLyS and preferably contain a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acids contained within the amino acid sequence of a BLyS polypeptide. Preferred polypeptides comprising immunogenic or antigenic epitopes are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof.

[0096] Non-limiting examples of antigenic polypeptides or peptides that can be used to generate BLyS-specific antibodies and which may be bound by the antibodies of the invention include: a polypeptide comprising, or alternatively consisting of, amino acid residues from about Phe-115 to about Leu-147 in SEQ ID NO:3228; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ile-150 to about Tyr-163 in SEQ ID NO:3228; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ser-171 to about Phe-194 in SEQ ID NO:3228; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Glu-223 to about Tyr-246 in SEQ ID NO:3228; and a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ser-271 to about Phe-278 in Figures 1A and 1B (SEQ ID NO:3228). In this context, "about" means the particularly recited ranges and ranges larger or smaller by several, a few, 5, 4, 3, 2 or 1 amino acid residues at either or both the amino- and carboxy-termini. These polypeptide fragments have been determined to bear antigenic epitopes of the BLyS polypeptide by the analysis of the Jameson-Wolf antigenic index, as disclosed Table 9, above.

[0097] Non-limiting examples of antigenic polypeptides or peptides that can be used to generate BLyS-specific antibodies and which may be bound by the antibodies of the invention include: a polypeptide comprising, or alternatively consisting of, amino acid residues from about Pro-32 to about Leu-47 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Glu-116 to about Ser-143 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Phe-153 to about Tyr-173 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Pro-218 to about Tyr-227 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ala-232 to about Gln-241 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ile-244 to about Ala-249 in SEQ ID NO:3229; and a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ser-252 to about Val-257 in SEQ ID NO:3229. In this context, "about" means the particularly recited ranges and ranges larger or smaller by several, a few, 5, 4, 3, 2 or 1 amino acid residues at either or both the amino- and carboxy-termini. These polypeptide fragments have been determined to bear antigenic epitopes of the BLyS polypeptide by the analysis of the Jameson-Wolf

antigenic index, as disclosed in Table 10 generated by the Protean eomponent of the DNA*STAR computer program (as set forth above).

[0098] BLyS epitope-bearing peptides and polypeptides may be produced by any conventional means. *See, e.g.*, Houghten, R. A. (1985) General method for the rapid solid-phase synthesis of large numbers of peptides: specificity of antigen-antibody interaction at the level of individual amino acids. *Proc. Natl. Acad. Sci. USA* *82*:5131-5135; this "Simultaneous Multiple Peptide Synthesis (SMPS)" process is further described in U. S. Patent No. 4,631,211 to Houghten et al. (1986).

[0099] The present invention encompasses antibodies that bind polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide having an amino acid sequence of SEQ ID NO:3228, or an epitope of the polypeptide sequence encoded by a polynucleotide sequence contained in ATCC deposit No. 97768, or encoded by a polynucleotide that hybridizes to cDNA sequence contained in ATCC deposit No. 97768 (e.g., under hybridization conditions described herein).

[0100] The present invention also encompasses antibodies that bind polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide having an amino acid sequence of SEQ ID NO:3229, or an epitope of the polypeptide sequence encoded by a polynucleotide sequence contained in ATCC deposit No. 203518, or encoded by a polynucleotide that hybridizes to the cDNA sequence contained in ATCC deposit No. 203518 (e.g., under hybridization conditions described herein).

[0101] The term "epitopes," as used herein, refers to portions of a polypeptide having antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human. In a preferred embodiment, the present invention encompasses antibodies that bind a polypeptide comprising an epitope. An "immunogenic epitope," as used herein, is defined as a portion of a protein that elicits an antibody response in an animal, as determined by any method known in the art, for example, by the methods for generating antibodies described *infra*. (See, for example, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998- 4002 (1983)). The term "antigenic epitope," as used herein, is defined as a portion of a protein to which an antibody can immunospecifically bind its antigen as determined by any method well known in the art, for example, by the immunoassays described herein. Immunospecific binding excludes non-specific binding but does not

necessarily exclude cross- reactivity with other antigens. Antigenic epitopes need not necessarily be immunogenic.

[0102] BLyS polypeptide fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, Proc. Natl. Acad. Sei. USA 82:5131-5135 (1985), further described in U.S. Patent No. 4,631,211).

[0103] In the present invention, antibodies of the present invention bind antigenic epitopes preferably containing a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acids. Preferred polypeptides comprising immunogenic or antigenic epitopes that may be bound by antibodies of the present invention are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof. Antigenic epitopes are useful, for example, to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. Preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these antigenic epitopes. Antigenic epitopes can be used as the target molecules in immunoassays. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe et al., Science 219:660-666 (1983)).

[0104] Similarly, immunogenic epitopes can be used, for example, to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., *supra*; Wilson et al., *supra*; Chow et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle et al., J. Gen. Virol. 66:2347-2354 (1985). Preferred immunogenic epitopes include the immunogenie epitopes diselosed herein, as well as any combination of two, three, four, five or more of these immunogenic epitopes. The polypeptides comprising one or more immunogenic epitopes of BLyS may be presented for elieiting an antibody response together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse), or, if the polypeptide is of sufficient length (at least about 25 amino acids), the polypeptide may be presented without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise

antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting).

[0105] Epitope-bearing BLyS polypeptides may be used to induce antibodies according to methods well known in the art including, but not limited to, *in vivo* immunization, *in vitro* immunization, and phage display methods. See, e.g., Sutcliffe et al., *supra*; Wilson et al., *supra*, and Bittle et al., J. Gen. Virol., 66:2347-2354 (1985). If *in vivo* immunization is used, animals may be immunized with free peptide; however, anti-peptide antibody titer may be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemocyanin (KLH) or tetanus toxoid. For instance, peptides containing cysteine residues may be coupled to a carrier using a linker such as maleimidobenzoyl-N-hydroxysuccinimide ester (MBS), while other peptides may be coupled to carriers using a more general linking agent such as glutaraldehyde. Animals such as rabbits, rats and mice are immunized with either free or carrier-coupled peptides, for instance, by intraperitoneal and/or intradermal injection of emulsions containing about 100 micrograms of peptide or carrier protein and Freund's adjuvant or any other adjuvant known for stimulating an immune response. Several booster injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-peptide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal may be increased by selection of anti-peptide antibodies, for instance, by adsorption to the peptide on a solid support and elution of the selected antibodies according to methods well known in the art.

[0106] As one of skill in the art will appreciate, and as discussed above, the antibodies of the present invention may bind polypeptides comprising an immunogenic or antigenic epitope fused to other polypeptide sequences. For example, the BLyS polypeptides may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM), or portions thereof (CH1, CH2, CH3, or any combination thereof and portions thereof), or albumin (including but not limited to recombinant human albumin or fragments or variants thereof (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)), resulting in chimeric polypeptides. Such fusion proteins may facilitate purification and may increase half-life *in vivo*. This has been shown for chimeric proteins

consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See, e.g., EP 394,827; Traunecker et al., Nature, 331:84-86 (1988). Enhanced delivery of an antigen across the epithelial barrier to the immune system has been demonstrated for antigens (e.g., insulin) eonjugated to an FcRn binding partner such as IgG or Fc fragments (see, e.g., PCT Publications WO 96/22024 and WO 99/04813). IgG Fusion proteins that have a disulfide-linked dimeric structure due to the IgG portion disulfide bonds have also been found to be more efficient in binding and neutralizing other molecules than monomeric polypeptides or fragments thereof alone. See, e.g., Fountoulakis et al., J. Biochem., 270:3958-3964 (1995). Nucleic acids encoding the above epitopes can also be recombined with a gene of interest as an epitope tag (e.g., the hemagglutinin ("HA") tag or flag tag) to aid in detection and purification of the expressed polypeptide. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht et al., 1991, Proc. Natl. Acad. Sci. USA 88:8972- 897). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the open reading frame of the gene is translationally fused to an amino-terminal tag consisting of six histidine residues. The tag serves as a matrix-binding domain for the fusion protein. Extracts from cells infected with the recombinant vaccinia virus are loaded onto Ni^{2+} nitriloacetic acid-agarose column and histidine-tagged proteins can be selectively eluted with imidazole-containing buffers.

[0107] In another embodiment, the antibodies of the present invention bind BLyS polypeptides and/or the epitope-bearing fragments thereof that are fused with a heterologous antigen (e.g., polypeptide, carbohydrate, phospholipid, or nucleic acid). In specific embodiments, the heterologous antigen is an immunogen.

[0108] In a more specifie embodiment, the heterologous antigen is the gp120 protein of HIV, or a fragment thereof.

[0109] In another embodiment, antibodies of the present invention bind BLyS polypeptides and/or the epitope-bearing fragments thereof that are fused with polypeptide sequences of another TNF ligand family member (or biologically active fragments or variants thereof). In a specific embodiment, the antibodies of the present invention bind BLyS polypeptides of the present invention are fused with a CD40L polypeptide sequence. In a preferred embodiment, the CD40L polypeptide sequence is soluble.

[0110] In another embodiment, antibodies of the present invention bind mutant BLyS polypeptides that have been generated by random mutagenesis of a polynucleotide encoding the BLyS polypeptide, by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, antibodies of the present invention bind one or more components, motifs, sections, parts, domains, fragments, etc., of BLyS recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous molecules are, for example, TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), AIM-II (International Publication No. WO 97/34911), APRIL (J. Exp. Med. 188(6):1185-1190), endokine-alpha (International Publication No. WO 98/07880), OPG, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-IBB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TR6 (International Publication No. WO 98/30694), TR7 (International Publication No. WO 98/41629), TRANK, TR9 (International Publication No. WO 98/56892), TR10 (International Publication No. WO 98/54202),312C2 (International Publication No. WO 98/06842), TR12, CAD, and v-FLIP. In further embodiments, the heterologous molecules are any member of the TNF family.

[0111] In another preferred embodiment, antibodies of the present invention bind BLyS polypeptides of the invention (including biologically active fragments or variants thereof), that are fused with soluble APRIL polypeptides (e.g., amino acid residues 105 through 250 of SEQ ID NO:3239), or biologically active fragments or variants thereof.

[0112] To improve or alter the characteristics of BLyS polypeptides, protein engineering may be employed. Recombinant DNA technology known to those skilled in the art can be used to create novel mutant proteins or "muteins including single or multiple amino acid substitutions, deletions, additions or fusion proteins. Such modified polypeptides can show, e.g., enhanced activity or increased stability. In addition, they may be purified in higher yields and show better solubility than the corresponding natural polypeptide, at least under certain purification and storage conditions. For instance, for

many proteins, including the extracellular domain or the mature form(s) of a secreted protein, it is known in the art that one or more amino acids may be deleted from the N-terminus or C-terminus without substantial loss of biological function. For instance, Ron et al., J. Biol. Chem., 268:2984-2988 (1993) reported modified KGF proteins that had heparin binding activity even if 3, 8, or 27 amino-terminal amino acid residues were missing. Accordingly, antibodies of the present invention may bind BLyS polypeptide mutants or variants generated by protein engineering.

[0113] In the present case, since the protein of the invention is a member of the TNF polypeptide family, deletions of N-terminal amino acids up to the Gly (G) residue at position 191 in SEQ ID NO:3228 may retain some biological activity such as, for example, the ability to stimulate lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, and cytotoxicity to appropriate target cells. Polypeptides having further N-terminal deletions including the Gly (G) residue would not be expected to retain biological activities because it is known that this residue in TNF-related polypeptides is in the beginning of the conserved domain required for biological activities. However, even if deletion of one or more amino acids from the N-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities may still be retained. Thus, the ability of the shortened protein to induce and/or bind to antibodies which recognize the complete or extracellular domain of the protein generally will be retained when less than the majority of the residues of the complete or extracellular domain of the protein are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete protein retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

[0114] Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of the BLyS of SEQ ID NO:3228, up to the glycine residue at position 191 (Gly-191 residue from the amino terminus). In particular, the present invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues n^1-285 of SEQ ID NO:3228, where n^1 is an integer in the range of the amino acid position of amino acid residues 2-190 of the amino acid sequence in SEQ ID NO:3228. More in particular, the invention provides antibodies that bind polypeptides

comprising, or alternatively consisting of, an amino aeid sequence selected from the group consisting of residues 2-285, 3-285, 4-285, 5-285, 6-285, 7-285, 8-285, 9-285, 10-285, 11-285, 12-285, 13-285, 14-285, 15-285, 16-285, 17-285, 18-285, 19-285, 20-285, 21-285, 22-285, 23-285, 24-285, 25-285, 26-285, 27-285, 28-285, 29-285, 30-285, 31-285, 32-285, 33-285, 34-285, 35-285, 36-285, 37-285, 38-285, 39-285, 40-285, 41-285, 42-285, 43-285, 44-285, 45-285, 46-285, 47-285, 48-285, 49-285, 50-285, 51-285, 52-285, 53-285, 54-285, 55-285, 56-285, 57-285, 58-285, 59-285, 60-285, 61-285, 62-285, 63-285, 64-285, 65-285, 66-285, 67-285, 68-285, 69-285, 70-285, 71-285, 72-285, 73-285, 74-285, 75-285, 76-285, 77-285, 78-285, 79-285, 80-285, 81-285, 82-285, 83-285, 84-285, 85-285, 86-285, 87-285, 88-285, 89-285, 90-285, 91-285, 92-285, 93-285, 94-285, 95-285, 96-285, 97-285, 98-285, 99-285, 100-285, 101-285, 102-285, 103-285, 104-285, 105-285, 106-285, 107-285, 108-285, 109-285, 110-285, 111-285, 112-285, 113-285, 114-285, 115-285, 116-285, 117-285, 118-285, 119-285, 120-285, 121-285, 122-285, 123-285, 124-285, 125-285, 126-285, 127-285, 128-285, 129-285, 130-285, 131-285, 132-285, 133-285, 134-285, 135-285, 136-285, 137-285, 138-285, 139-285, 140-285, 141-285, 142-285, 143-285, 144-285, 145-285, 146-285, 147-285, 148-285, 149-285, 150-285, 151-285, 152-285, 153-285, 154-285, 155-285, 156-285, 157-285, 158-285, 159-285, 160-285, 161-285, 162-285, 163-285, 164-285, 165-285, 166-285, 167-285, 168-285, 169-285, 170-285, 171-285, 172-285, 173-285, 174-285, 175-285, 176-285, 177-285, 178-285, 179-285, 180-285, 181-285, 182-285, 183-285, 184-285, 185-285, 186-285, 187-285, 188-285, 189-285, and 190-285 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

[0115] Furthermore, since the predicted extracellular domain of the BLyS polypeptides of the invention may itself elicit biological activity, deletions of N- and C-terminal amino acid residues from the predicted extracellular region of the polypeptide (spanning positions Gln-73 to Leu-285 of SEQ ID NO:3228) may retain some biological activity such as, for example, ligand binding, stimulation of lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, and modulation of cell replication or modulation of target cell activities. However, even if deletion of one or more amino acids

from the N-terminus of the predicted extracellular domain of a BLyS polypeptide results in modification or loss of one or more biological functions of the polypeptide, other functional activities may still be retained. Thus, the ability of the shortened polypeptides to induce and/or bind to antibodies which recognize the complete or mature or extracellular domains of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature or extracellular domains of the polypeptides are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

[0116] Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of BLyS shown in SEQ ID NO:3228, up to the glycine residue at position number 280. In particular, the present invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues n^2-285 of SEQ ID NO:3228, where n^2 is an integer in the range of the amino acid position of amino acid residues 73-280 in SEQ ID NO:3228, and 73 is the position of the first residue from the N-terminus of the predicted extracellular domain of the BLyS polypeptide (disclosed in SEQ ID NO:3228). More in particular, in certain embodiments, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues of Q-73 to L-285; G-74 to L-285; D-75 to L-285; L-76 to L-285; A-77 to L-285; S-78 to L-285; L-79 to L-285; R-80 to L-285; A-81 to L-285; E-82 to L-285; L-83 to L-285; Q-84 to L-285; G-85 to L-285; H-86 to L-285; H-87 to L-285; A-88 to L-285; E-89 to L-285; K-90 to L-285; L-91 to L-285; P-92 to L-285; A-93 to L-285; G-94 to L-285; A-95 to L-285; G-96 to L-285; A-97 to L-285; P-98 to L-285; K-99 to L-285; A-100 to L-285; G-101 to L-285; L-102 to L-285; E-103 to L-285; E-104 to L-285; A-105 to L-285; P-106 to L-285; A-107 to L-285; V-108 to L-285; T-109 to L-285; A-110 to L-285; G-111 to L-285; L-112 to L-285; K-113 to L-285; I-114 to L-285; F-115 to L-285; E-116 to L-285; P-117 to L-285; P-118 to L-285; A-119 to L-285; P-120 to L-285; G-121 to L-285; E-122 to L-285; G-123 to L-285; N-124 to L-285; S-125 to L-285; S-126 to L-285; Q-127 to L-285; N-128 to L-285; S-129 to L-285; R-130 to L-285; N-131 to L-285; K-132 to L-285; R-133 to L-285; A-134 to L-285; V-135 to L-285; Q-136 to L-285; G-137 to

L-285; P-138 to L-285; E-139 to L-285; E-140 to L-285; T-141 to L-285; V-142 to L-285; T-143 to L-285; Q-144 to L-285; D-145 to L-285; C-146 to L-285; L-147 to L-285; Q-148 to L-285; L-149 to L-285; I-150 to L-285; A-151 to L-285; D-152 to L-285; S-153 to L-285; E-154 to L-285; T-155 to L-285; P-156 to L-285; T-157 to L-285; I-158 to L-285; Q-159 to L-285; K-160 to L-285; G-161 to L-285; S-162 to L-285; Y-163 to L-285; T-164 to L-285; F-165 to L-285; V-166 to L-285; P-167 to L-285; W-168 to L-285; L-169 to L-285; L-170 to L-285; S-171 to L-285; F-172 to L-285; K-173 to L-285; R-174 to L-285; G-175 to L-285; S-176 to L-285; A-177 to L-285; L-178 to L-285; E-179 to L-285; E-180 to L-285; K-181 to L-285; E-182 to L-285; N-183 to L-285; K-184 to L-285; I-185 to L-285; L-186 to L-285; V-187 to L-285; K-188 to L-285; E-189 to L-285; T-190 to L-285; G-191 to L-285; Y-192 to L-285; F-193 to L-285; F-194 to L-285; I-195 to L-285; Y-196 to L-285; G-197 to L-285; Q-198 to L-285; V-199 to L-285; L-200 to L-285; Y-201 to L-285; T-202 to L-285; D-203 to L-285; K-204 to L-285; T-205 to L-285; Y-206 to L-285; A-207 to L-285; M-208 to L-285; G-209 to L-285; H-210 to L-285; L-211 to L-285; I-212 to L-285; Q-213 to L-285; R-214 to L-285; K-215 to L-285; K-216 to L-285; V-217 to L-285; H-218 to L-285; V-219 to L-285; F-220 to L-285; G-221 to L-285; D-222 to L-285; E-223 to L-285; L-224 to L-285; S-225 to L-285; L-226 to L-285; V-227 to L-285; T-228 to L-285; L-229 to L-285; F-230 to L-285; R-231 to L-285; C-232 to L-285; I-233 to L-285; Q-234 to L-285; N-235 to L-285; M-236 to L-285; P-237 to L-285; E-238 to L-285; T-239 to L-285; L-240 to L-285; P-241 to L-285; N-242 to L-285; N-243 to L-285; S-244 to L-285; C-245 to L-285; Y-246 to L-285; S-247 to L-285; A-248 to L-285; G-249 to L-285; I-250 to L-285; A-251 to L-285; K-252 to L-285; L-253 to L-285; E-254 to L-285; E-255 to L-285; G-256 to L-285; D-257 to L-285; E-258 to L-285; L-259 to L-285; Q-260 to L-285; L-261 to L-285; A-262 to L-285; I-263 to L-285; P-264 to L-285; R-265 to L-285; E-266 to L-285; N-267 to L-285; A-268 to L-285; Q-269 to L-285; I-270 to L-285; S-271 to L-285; L-272 to L-285; D-273 to L-285; G-274 to L-285; D-275 to L-285; V-276 to L-285; T-277 to L-285; F-278 to L-285; F-279 to L-285; and G-280 to L-285 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

[0117] Highly preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence least 80%, 85%, 90% identical and more preferably at least 95%, 96%, 97%, 98%, 99% or 100% identical to BLyS polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228.

[0118] Preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 90% identical to a BLyS polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228. More preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 95% identical to a BLyS polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228. More preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 96% identical to a BLyS polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228.

[0119] Additionally, more preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 97% to a BLyS polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228. Additionally, more preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 98% to a BLyS polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228. Additionally, more preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 99% identical to BLyS polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228.

[0120] In specific embodiments, antibodies of the present invention bind polypeptides comprising, or alternatively consisting of, one of the following N-terminally deleted polypeptide fragments of BLyS: amino acid residues Ala-71 through Leu-285, amino acid residues Ala-81 through Leu-285, amino acid residues Leu-112 through Leu-285, amino

acid residues Ala-134 through Leu-285, amino acid residues Leu-147 through Leu-285, and amino acid residues Gly-161 through Leu-285 of SEQ ID NO:3228.

[0121] Similarly, many examples of biologically functional C-terminal deletion polypeptides are known. For instance, Interferon gamma shows up to ten times higher activities by deleting 8-10 amino acid residues from the carboxy terminus of the protein (Döbeli et al., *J. Biotechnology* 7:199-216 (1988). Since the present protein is a member of the TNF polypeptide family, deletions of C-terminal amino acids up to the leucine residue at position 284 are expected to retain most if not all biological activity such as, for example, ligand binding, the ability to stimulate lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, and modulation of cell replication. Polypeptides having deletions of up to about 10 additional C-terminal residues (i.e., up to the glycine residue at position 274) also may retain some activity such as receptor binding, although sueh polypeptides would lack a portion of the conserved TNF domain which extends to about Leu-284 of SEQ ID NO:3228. However, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities may still be retained. Thus, the ability of the shortened protein to induce and/or bind to antibodies which recognize the complete or mature protein generally will be retained when less than the majority of the residues of the complete or mature protein are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete protein retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

[0122] Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the BLyS polypeptide of SEQ ID NO:3228, up to the glycine residue at position 274 (Gly-274). In particular, the present invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues 1-m^1 of the amino acid sequence in SEQ ID NO:3228, where m^1 is any integer in the range of the amino acid position of amino acid residues 274-284 in SEQ ID NO:3228. More in particular, the invention provides antibodies that bind BLyS polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues 1-274, 1-275, 1-276, 1-277, 1-278, 1-279, 1-280, 1-281, 1-282,

1-283 and 1-284 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

[0123] Also provided are antibodies that bind BLyS polypeptides comprising, or alternatively consisting of, BLyS polypeptides with one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues n^1-m^1 of SEQ ID NO:3228, where n^1 and m^1 are integers as defined above. Also included are antibodies that bind a polypeptide comprising, or alternatively consisting of, a portion of the complete BLyS amino acid sequence encoded by the deposited cDNA clone contained in ATCC Accession No. 97768 where this portion excludes from 1 to 190 amino acids from the amino terminus or from 1 to 11 amino acids from the C-terminus of the complete amino aeid sequence (or any combination of these N-terminal and C-terminal deletions) encoded by the cDNA clone in the deposited plasmid.

[0124] Similarly, deletions of C-terminal amino acid residues of the predicted extracellular domain of BLyS up to the leucine residue at position 79 of SEQ ID NO:3228 may retain some biological activity, such as, for example, ligand binding, stimulation of lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, and modulation of cell replication or modulation of target cell activities. Polypeptides having further C-terminal deletions ineluding Leu-79 of SEQ ID NO:3228 would not be expected to retain biological activities.

[0125] However, even if deletion of one or more amino acids from the C-terminus of a polypeptide results in modification or loss of one or more biological functions of the polypeptide, other functional activities may still be retained. Thus, the ability of the shortened polypeptide to induee and/or bind to antibodies which recognize the complete, mature or extracellular forms of the polypeptide generally will be retained when less than the majority of the residues of the complete, mature or extracellular forms of the polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of the predicted extracellular domain retains such immunologie activities can readily be determined by routine methods described herein and otherwise known in the art.

[0126] Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the predicted extracellular domain of BLyS polypeptide shown in SEQ ID NO:3228, up to the leucine residue at position 79 of SEQ ID NO:3228. In particular, the present invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues 73-m^2 of the amino acid sequence in SEQ ID NO:3228, where m^2 is any integer in the range of the amino acid position of amino acid residues 79 to 285 in the amino acid sequence in SEQ ID NO:3228, and residue 78 is the position of the first residue at the C- terminus of the predicted extracellular domain of the BLyS polypeptide (disclosed in SEQ ID NO:3228). More in particular, in certain embodiments, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues Q-73 to Leu-285; Q-73 to L-284; Q-73 to K-283; Q-73 to L-282; Q-73 to A-281; Q-73 to G-280; Q-73 to F-279; Q-73 to F-278; Q-73 to T-277; Q-73 to V-276; Q-73 to D-275; Q-73 to G-274; Q-73 to D-273; Q-73 to L-272; Q-73 to S-271; Q-73 to I-270; Q-73 to Q-269; Q-73 to A-268; Q-73 to N-267; Q-73 to E-266; Q-73 to R-265; Q-73 to P-264; Q-73 to I-263; Q-73 to A-262; Q-73 to L-261; Q-73 to Q-260; Q-73 to L-259; Q-73 to E-258; Q-73 to D-257; Q-73 to G-256; Q-73 to E-255; Q-73 to E-254; Q-73 to L-253; Q-73 to K-252; Q-73 to A-251; Q-73 to I-250; Q-73 to G-249; Q-73 to A-248; Q-73 to S-247; Q-73 to Y-246; Q-73 to C-245; Q-73 to S-244; Q-73 to N-243; Q-73 to N-242; Q-73 to P-241; Q-73 to L-240; Q-73 to T-239; Q-73 to E-238; Q-73 to P-237; Q-73 to M-236; Q-73 to N-235; Q-73 to Q-234; Q-73 to I-233; Q-73 to C-232; Q-73 to R-231; Q-73 to F-230; Q-73 to L-229; Q-73 to T-228; Q-73 to V-227; Q-73 to L-226; Q-73 to S-225; Q-73 to L-224; Q-73 to E-223; Q-73 to D-222; Q-73 to G-221; Q-73 to F-220; Q-73 to V-219; Q-73 to H-218; Q-73 to V-217; Q-73 to K-216; Q-73 to K-215; Q-73 to R-214; Q-73 to Q-213; Q-73 to I-212; Q-73 to L-211; Q-73 to H-210; Q-73 to G-209; Q-73 to M-208; Q-73 to A-207; Q-73 to Y-206; Q-73 to T-205; Q-73 to K-204; Q-73 to D-203; Q-73 to T-202; Q-73 to Y-201; Q-73 to L-200; Q-73 to V-199; Q-73 to Q-198; Q-73 to G-197; Q-73 to Y-196; Q-73 to I-195; Q-73 to F-194; Q-73 to F-193; Q-73 to Y-192; Q-73 to G-191; Q-73 to T-190; Q-73 to E-189; Q-73 to K-188; Q-73 to V-187; Q-73 to L-186; Q-73 to I-185; Q-73 to K-184; Q-73 to N-183; Q-73 to E-182; Q-73 to K-181; Q-73 to E-180; Q-73 to E-179; Q-73 to L-178;

Q-73 to A-177; Q-73 to S-176; Q-73 to G-175; Q-73 to R-174; Q-73 to K-173; Q-73 to F-172; Q-73 to S-171; Q-73 to L-170; Q-73 to L-169; Q-73 to W-168; Q-73 to P-167; Q-73 to V-166; Q-73 to F-165; Q-73 to T-164; Q-73 to Y-163; Q-73 to S-162; Q-73 to G-161; Q-73 to K-160; Q-73 to Q-159; Q-73 to I-158; Q-73 to T-157; Q-73 to P-156; Q-73 to T-155; Q-73 to E-154; Q-73 to S-153; Q-73 to D-152; Q-73 to A-151; Q-73 to I-150; Q-73 to L-149; Q-73 to Q-148; Q-73 to L-147; Q-73 to C-146; Q-73 to D-145; Q-73 to Q-144; Q-73 to T-143; Q-73 to V-142; Q-73 to T-141; Q-73 to E-140; Q-73 to E-139; Q-73 to P-138; Q-73 to G-137; Q-73 to Q-136; Q-73 to V-135; Q-73 to A-134; Q-73 to R-133; Q-73 to K-132; Q-73 to N-131; Q-73 to R-130; Q-73 to S-129; Q-73 to N-128; Q-73 to Q-127; Q-73 to S-126; Q-73 to S-125; Q-73 to N-124; Q-73 to G-123; Q-73 to E-122; Q-73 to G-121; Q-73 to P-120; Q-73 to A-119; Q-73 to P-118; Q-73 to P-117; Q-73 to E-116; Q-73 to F-115; Q-73 to I-114; Q-73 to K-113; Q-73 to L-112; Q-73 to G-111; Q-73 to A-110; Q-73 to T-109; Q-73 to V-108; Q-73 to A-107; Q-73 to P-106; Q-73 to A-105; Q-73 to E-104; Q-73 to E-103; Q-73 to L-102; Q-73 to G-101; Q-73 to A-100; Q-73 to K-99; Q-73 to P-98; Q-73 to A-97; Q-73 to G-96; Q-73 to A-95; Q-73 to G-94; Q-73 to A-93; Q-73 to P-92; Q-73 to L-91; Q-73 to K-90; Q-73 to E-89; Q-73 to A-88; Q-73 to H-87; Q-73 to H-86; Q-73 to G-85; Q-73 to Q-84; Q-73 to L-83; Q-73 to E-82; Q-73 to A-81; Q-73 to R-80; and Q-73 to L-79 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

[0127] The invention also provides antibodies that bind polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini of the predicted extracellular domain of BLyS, which may be described generally as having residues n^2-m^2 of SEQ ID NO:3228 where n^2 and m^2 are integers as defined above.

[0128] In another embodiment, antibodies of the present invention bind polypeptides consisting of a portion of the extracellular domain of the BLyS amino acid sequence encoded by the cDNA plasmid contained in the deposit having ATCC accession no. 97768, where this portion excludes from 1 to about 206 amino acids from the amino terminus of the extracellular domain of the amino acid sequence encoded by the cDNA plasmid contained in the deposit having ATCC accession no. 97768, or from 1 to about

206 amino acids from the carboxy terminus of the extracellular domain of the amino acid sequence encoded by the cDNA plasmid contained in the deposit having ATCC accession no. 97768, or any combination of the above amino terminal and carboxy terminal deletions, of the entire extracellular domain of the amino acid sequence encoded by the cDNA plasmid contained in the deposit having ATCC accession no. 97768.

[0129] As mentioned above, even if deletion of one or more amino acids from the N-terminus of a polypeptide results in modification or loss of one or more functional activities (e.g., biological activity) of the polypeptide, other functions or biological activities may still be retained. Thus, the ability of a shortened BLyS mutein to induce and/or bind to antibodies which recognize the full-length or mature forms or the extracellular domain of the polypeptide generally will be retained when less than the majority of the residues of the full-length or mature or extracellular domain of the polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a BLyS mutein with a large number of deleted N-terminal amino acid residues may retain some functional (e.g., biological or immunogenic) activities. In fact, peptides composed of as few as six BLyS amino acid residues may often evoke an immune response.

[0130] Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the predicted full-length amino acid sequence of the BLyS shown in SEQ ID NO:3228, up to the glycine residue at position number 280 of the sequence shown SEQ ID NO:3228 and polynucleotides encoding such polypeptides. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues n^3-285 of the sequence shown in SEQ ID NO:3228, where n^3 is an integer in the range of the amino acid position of amino acid residues 1 to 280 of the amino acid sequence in SEQ ID NO:3228.

[0131] More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues of D-2 to L-285; D-3 to L-285; S-4 to L-285; T-5 to L-285; E-6 to L-285; R-7 to L-285; E-8 to L-285; Q-9 to L-285; S-10 to L-285; R-11 to L-285; L-12 to

L-285; T-13 to L-285; S-14 to L-285; C-15 to L-285; L-16 to L-285; K-17 to L-285; K-18 to L-285; R-19 to L-285; E-20 to L-285; E-21 to L-285; M-22 to L-285; K-23 to L-285; L-24 to L-285; K-25 to L-285; E-26 to L-285; C-27 to L-285; V-28 to L-285; S-29 to L-285; I-30 to L-285; L-31 to L-285; P-32 to L-285; R-33 to L-285; K-34 to L-285; E-35 to L-285; S-36 to L-285; P-37 to L-285; S-38 to L-285; V-39 to L-285; R-40 to L-285; S-41 to L-285; S-42 to L-285; K-43 to L-285; D-44 to L-285; G-45 to L-285; K-46 to L-285; L-47 to L-285; L-48 to L-285; A-49 to L-285; A-50 to L-285; T-51 to L-285; L-52 to L-285; L-53 to L-285; L-54 to L-285; A-55 to L-285; L-56 to L-285; L-57 to L-285; S-58 to L-285; C-59 to L-285; C-60 to L-285; L-61 to L-285; T-62 to L-285; V-63 to L-285; V-64 to L-285; S-65 to L-285; F-66 to L-285; Y-67 to L-285; Q-68 to L-285; V-69 to L-285; A-70 to L-285; A-71 to L-285; L-72 to L-285; Q-73 to L-285; G-74 to L-285; D-75 to L-285; L-76 to L-285; A-77 to L-285; S-78 to L-285; L-79 to L-285; R-80 to L-285; A-81 to L-285; E-82 to L-285; L-83 to L-285; Q-84 to L-285; G-85 to L-285; H-86 to L-285; H-87 to L-285; A-88 to L-285; E-89 to L-285; K-90 to L-285; L-91 to L-285; P-92 to L-285; A-93 to L-285; G-94 to L-285; A-95 to L-285; G-96 to L-285; A-97 to L-285; P-98 to L-285; K-99 to L-285; A-100 to L-285; G-101 to L-285; L-102 to L-285; E-103 to L-285; E-104 to L-285; A-105 to L-285; P-106 to L-285; A-107 to L-285; V-108 to L-285; T-109 to L-285; A-110 to L-285; G-111 to L-285; L-112 to L-285; K-113 to L-285; I-114 to L-285; F-115 to L-285; E-116 to L-285; P-117 to L-285; P-118 to L-285; A-119 to L-285; P-120 to L-285; G-121 to L-285; E-122 to L-285; G-123 to L-285; N-124 to L-285; S-125 to L-285; S-126 to L-285; Q-127 to L-285; N-128 to L-285; S-129 to L-285; R-130 to L-285; N-131 to L-285; K-132 to L-285; R-133 to L-285; A-134 to L-285; V-135 to L-285; Q-136 to L-285; G-137 to L-285; P-138 to L-285; E-139 to L-285; E-140 to L-285; T-141 to L-285; V-142 to L-285; T-143 to L-285; Q-144 to L-285; D-145 to L-285; C-146 to L-285; L-147 to L-285; Q-148 to L-285; L-149 to L-285; I-150 to L-285; A-151 to L-285; D-152 to L-285; S-153 to L-285; E-154 to L-285; T-155 to L-285; P-156 to L-285; T-157 to L-285; I-158 to L-285; Q-159 to L-285; K-160 to L-285; G-161 to L-285; S-162 to L-285; Y-163 to L-285; T-164 to L-285; F-165 to L-285; V-166 to L-285; P-167 to L-285; W-168 to L-285; L-169 to L-285; L-170 to L-285; S-171 to L-285; F-172 to L-285; K-173 to L-285; R-174 to L-285; G-175 to L-285; S-176 to L-285; A-177 to L-285; L-178 to L-285; E-179 to L-285; E-180 to L-285; K-181 to L-285; E-182 to L-285; N-183 to L-285; K-184 to L-285; I-185 to L-285; L-186 to

L-285; V-187 to L-285; K-188 to L-285; E-189 to L-285; T-190 to L-285; G-191 to L-285; Y-192 to L-285; F-193 to L-285; F-194 to L-285; I-195 to L-285; Y-196 to L-285; G-197 to L-285; Q-198 to L-285; V-199 to L-285; L-200 to L-285; Y-201 to L-285; T-202 to L-285; D-203 to L-285; K-204 to L-285; T-205 to L-285; Y-206 to L-285; A-207 to L-285; M-208 to L-285; G-209 to L-285; H-210 to L-285; L-211 to L-285; I-212 to L-285; Q-213 to L-285; R-214 to L-285; K-215 to L-285; K-216 to L-285; V-217 to L-285; H-218 to L-285; V-219 to L-285; F-220 to L-285; G-221 to L-285; D-222 to L-285; E-223 to L-285; L-224 to L-285; S-225 to L-285; L-226 to L-285; V-227 to L-285; T-228 to L-285; L-229 to L-285; F-230 to L-285; R-231 to L-285; C-232 to L-285; I-233 to L-285; Q-234 to L-285; N-235 to L-285; M-236 to L-285; P-237 to L-285; E-238 to L-285; T-239 to L-285; L-240 to L-285; P-241 to L-285; N-242 to L-285; N-243 to L-285; S-244 to L-285; C-245 to L-285; Y-246 to L-285; S-247 to L-285; A-248 to L-285; G-249 to L-285; I-250 to L-285; A-251 to L-285; K-252 to L-285; L-253 to L-285; E-254 to L-285; E-255 to L-285; G-256 to L-285; D-257 to L-285; E-258 to L-285; L-259 to L-285; Q-260 to L-285; L-261 to L-285; A-262 to L-285; I-263 to L-285; P-264 to L-285; R-265 to L-285; E-266 to L-285; N-267 to L-285; A-268 to L-285; Q-269 to L-285; I-270 to L-285; S-271 to L-285; L-272 to L-285; D-273 to L-285; G-274 to L-285; D-275 to L-285; V-276 to L-285; T-277 to L-285; F-278 to L-285; F-279 to L-285; and G-280 to L-285 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

[0132] Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more functional activities (e.g., biological activity) of the protein, other functional activities may still be retained. Thus, the ability of a shortened BLyS mutein to induce and/or bind to antibodies which recognize the complete or mature form or the extracellular domain of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature form or the extracellular domain of the polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a BLyS

mutein with a large number of deleted C-terminal amino acid residues may retain some functional (e.g., biological or immunogenic) activities. In fact, peptides composed of as few as six BLyS amino acid residues may often evoke an immune response.

[0133] Accordingly, the present invention further provides in another embodiment, antibodies that bind polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the BLyS shown in SEQ ID NO:3228, up to the glutamic acid residue at position number 6, and polynucleotides encoding such polypeptides. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues 1-m^3 of SEQ ID NO:3228, where m^3 is an integer in the range of the amino acid position of amino acid residues 6-284 of the amino acid sequence in SEQ ID NO:3228.

[0134] More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues M-1 to L-284; M-1 to K-283; M-1 to L-282; M-1 to A-281; M-1 to G-280; M-1 to F-279; M-1 to F-278; M-1 to T-277; M-1 to V-276; M-1 to D-275; M-1 to G-274; M-1 to D-273; M-1 to L-272; M-1 to S-271; M-1 to I-270; M-1 to Q-269; M-1 to A-268; M-1 to N-267; M-1 to E-266; M-1 to R-265; M-1 to P-264; M-1 to I-263; M-1 to A-262; M-1 to L-261; M-1 to Q-260; M-1 to L-259; M-1 to E-258; M-1 to D-257; M-1 to G-256; M-1 to E-255; M-1 to E-254; M-1 to L-253; M-1 to K-252; M-1 to A-251; M-1 to I-250; M-1 to G-249; M-1 to A-248; M-1 to S-247; M-1 to Y-246; M-1 to C-245; M-1 to S-244; M-1 to N-243; M-1 to N-242; M-1 to P-241; M-1 to L-240; M-1 to T-239; M-1 to E-238; M-1 to P-237; M-1 to M-236; M-1 to N-235; M-1 to Q-234; M-1 to I-233; M-1 to C-232; M-1 to R-231; M-1 to F-230; M-1 to L-229; M-1 to T-228; M-1 to V-227; M-1 to L-226; M-1 to S-225; M-1 to L-224; M-1 to E-223; M-1 to D-222; M-1 to G-221; M-1 to F-220; M-1 to V-219; M-1 to H-218; M-1 to V-217; M-1 to K-216; M-1 to K-215; M-1 to R-214; M-1 to Q-213; M-1 to I-212; M-1 to L-211; M-1 to H-210; M-1 to G-209; M-1 to M-208; M-1 to A-207; M-1 to Y-206; M-1 to T-205; M-1 to K-204; M-1 to D-203; M-1 to T-202; M-1 to Y-201; M-1 to L-200; M-1 to V-199; M-1 to Q-198; M-1 to G-197; M-1 to Y-196; M-1 to I-195; M-1 to F-194; M-1 to F-193; M-1 to Y-192; M-1 to G-191; M-1 to T-190; M-1 to E-189; M-1 to K-188; M-1 to V-187; M-1 to L-186; M-1 to I-185; M-1 to K-184; M-1 to N-183; M-1 to E-182; M-1 to K-181; M-1 to E-180; M-1 to E-179; M-1 to L-178; M-1 to A-177; M-1 to S-176; M-1 to G-175; M-1 to R-174; M-1 to K-173; M-1 to

F-172; M-1 to S-171; M-1 to L-170; M-1 to L-169; M-1 to W-168; M-1 to P-167; M-1 to V-166; M-1 to F-165; M-1 to T-164; M-1 to Y-163; M-1 to S-162; M-1 to G-161; M-1 to K-160; M-1 to Q-159; M-1 to I-158; M-1 to T-157; M-1 to P-156; M-1 to T-155; M-1 to E-154; M-1 to S-153; M-1 to D-152; M-1 to A-151; M-1 to I-150; M-1 to L-149; M-1 to Q-148; M-1 to L-147; M-1 to C-146; M-1 to D-145; M-1 to Q-144; M-1 to T-143; M-1 to V-142; M-1 to T-141; M-1 to E-140; M-1 to E-139; M-1 to P-138; M-1 to G-137; M-1 to Q-136; M-1 to V-135; M-1 to A-134; M-1 to R-133; M-1 to K-132; M-1 to N-131; M-1 to R-130; M-1 to S-129; M-1 to N-128; M-1 to Q-127; M-1 to S-126; M-1 to S-125; M-1 to N-124; M-1 to G-123; M-1 to E-122; M-1 to G-121; M-1 to P-120; M-1 to A-119; M-1 to P-118; M-1 to P-117; M-1 to E-116; M-1 to F-115; M-1 to I-114; M-1 to K-113; M-1 to L-112; M-1 to G-111; M-1 to A-110; M-1 to T-109; M-1 to V-108; M-1 to A-107; M-1 to P-106; M-1 to A-105; M-1 to E-104; M-1 to E-103; M-1 to L-102; M-1 to G-101; M-1 to A-100; M-1 to K-99; M-1 to P-98; M-1 to A-97; M-1 to G-96; M-1 to A-95; M-1 to G-94; M-1 to A-93; M-1 to P-92; M-1 to L-91; M-1 to K-90; M-1 to E-89; M-1 to A-88; M-1 to H-87; M-1 to H-86; M-1 to G-85; M-1 to Q-84; M-1 to L-83; M-1 to E-82; M-1 to A-81; M-1 to R-80; M-1 to L-79; M-1 to S-78; M-1 to A-77; M-1 to L-76; M-1 to D-75; M-1 to G-74; M-1 to Q-73; M-1 to L-72; M-1 to A-71; M-1 to A-70; M-1 to V-69; M-1 to Q-68; M-1 to Y-67; M-1 to F-66; M-1 to S-65; M-1 to V-64; M-1 to V-63; M-1 to T-62; M-1 to L-61; M-1 to C-60; M-1 to C-59; M-1 to S-58; M-1 to L-57; M-1 to L-56; M-1 to A-55; M-1 to L-54; M-1 to L-53; M-1 to L-52; M-1 to T-51; M-1 to A-50; M-1 to A-49; M-1 to L-48; M-1 to L-47; M-1 to K-46; M-1 to G-45; M-1 to D-44; M-1 to K-43; M-1 to S-42; M-1 to S-41; M-1 to R-40; M-1 to V-39; M-1 to S-38; M-1 to P-37; M-1 to S-36; M-1 to E-35; M-1 to K-34; M-1 to R-33; M-1 to P-32; M-1 to L-31; M-1 to I-30; M-1 to S-29; M-1 to V-28; M-1 to C-27; M-1 to E-26; M-1 to K-25; M-1 to L-24; M-1 to K-23; M-1 to M-22; M-1 to E-21; M-1 to E-20; M-1 to R-19; M-1 to K-18; M-1 to K-17; M-1 to L-16; M-1 to C-15; M-1 to S-14; M-1 to T-13; M-1 to L-12; M-1 to R-11; M-1 to S-10; M-1 to Q-9; M-1 to E-8; M-1 to R-7; and M-1 to E-6 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

[0135] The invention also provides antibodies that bind polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini of a BLyS polypeptide, which may be described generally as having residues n^3-m^3 of SEQ ID NO:3228, where n^3 and m^3 are integers as defined above.

[0136] Furthermore, since the predicted extracellular domain of the BLyS polypeptide of SEQ ID NO:3229 may itself elicit functional activity (e.g., biological activity), deletions of N- and C-terminal amino acid residues from the predicted extracellular region of the polypeptide at positions Gln-73 to Leu-266 of SEQ ID NO:3229 may retain some functional activity, such as, for example, ligand binding, to stimulation of lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, modulation of cell replication, modulation of target cell activities and/or immunogenicity. However, even if deletion of one or more amino acids from the N-terminus of the predicted extracellular domain of a BLyS polypeptide results in modification or loss of one or more functional activities of the polypeptide, other functional activities may still be retained. Thus, the ability of the shortened polypeptides to induce and/or bind to antibodies which recognize the complete or mature or extracellular domains of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature or extracellular domains of the polypeptides are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

[0137] Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of BLyS shown in SEQ ID NO:3229, up to the glycine residue at position number 261. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues n^4-266 of SEQ ID NO:3229, where n^4 is an integer in the range of the amino acid position of amino acid residues 73-261 of the amino acid sequence in SEQ ID NO:3229, and 261 is the position of the first residue from the N-terminus of the predicted extracellular domain BLyS polypeptide (shown in SEQ ID NO:3229).

[0138] More in particular, in certain embodiments, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence

selected from the group consisting of residues of Q-73 to L-266; G-74 to L-266; D-75 to L-266; L-76 to L-266; A-77 to L-266; S-78 to L-266; L-79 to L-266; R-80 to L-266; A-81 to L-266; E-82 to L-266; L-83 to L-266; Q-84 to L-266; G-85 to L-266; H-86 to L-266; H-87 to L-266; A-88 to L-266; E-89 to L-266; K-90 to L-266; L-91 to L-266; P-92 to L-266; A-93 to L-266; G-94 to L-266; A-95 to L-266; G-96 to L-266; A-97 to L-266; P-98 to L-266; K-99 to L-266; A-100 to L-266; G-101 to L-266; L-102 to L-266; E-103 to L-266; E-104 to L-266; A-105 to L-266; P-106 to L-266; A-107 to L-266; V-108 to L-266; T-109 to L-266; A-110 to L-266; G-111 to L-266; L-112 to L-266; K-113 to L-266; I-114 to L-266; F-115 to L-266; E-116 to L-266; P-117 to L-266; P-118 to L-266; A-119 to L-266; P-120 to L-266; G-121 to L-266; E-122 to L-266; G-123 to L-266; N-124 to L-266; S-125 to L-266; S-126 to L-266; Q-127 to L-266; N-128 to L-266; S-129 to L-266; R-130 to L-266; N-131 to L-266; K-132 to L-266; R-133 to L-266; A-134 to L-266; V-135 to L-266; Q-136 to L-266; G-137 to L-266; P-138 to L-266; E-139 to L-266; E-140 to L-266; T-141 to L-266; G-142 to L-266; S-143 to L-266; Y-144 to L-266; T-145 to L-266; F-146 to L-266; V-147 to L-266; P-148 to L-266; W-149 to L-266; L-150 to L-266; L-151 to L-266; S-152 to L-266; F-153 to L-266; K-154 to L-266; R-155 to L-266; G-156 to L-266; S-157 to L-266; A-158 to L-266; L-159 to L-266; E-160 to L-266; E-161 to L-266; K-162 to L-266; E-163 to L-266; N-164 to L-266; K-165 to L-266; I-166 to L-266; L-167 to L-266; V-168 to L-266; K-169 to L-266; E-170 to L-266; T-171 to L-266; G-172 to L-266; Y-173 to L-266; F-174 to L-266; F-175 to L-266; I-176 to L-266; Y-177 to L-266; G-178 to L-266; Q-179 to L-266; V-180 to L-266; L-181 to L-266; Y-182 to L-266; T-183 to L-266; D-184 to L-266; K-185 to L-266; T-186 to L-266; Y-187 to L-266; A-188 to L-266; M-189 to L-266; G-190 to L-266; H-191 to L-266; L-192 to L-266; I-193 to L-266; Q-194 to L-266; R-195 to L-266; K-196 to L-266; K-197 to L-266; V-198 to L-266; H-199 to L-266; V-200 to L-266; F-201 to L-266; G-202 to L-266; D-203 to L-266; E-204 to L-266; L-205 to L-266; S-206 to L-266; L-207 to L-266; V-208 to L-266; T-209 to L-266; L-210 to L-266; F-211 to L-266; R-212 to L-266; C-213 to L-266; I-214 to L-266; Q-215 to L-266; N-216 to L-266; M-217 to L-266; P-218 to L-266; E-219 to L-266; T-220 to L-266; L-221 to L-266; P-222 to L-266; N-223 to L-266; N-224 to L-266; S-225 to L-266; C-226 to L-266; Y-227 to L-266; S-228 to L-266; A-229 to L-266; G-230 to L-266; I-231 to L-266; A-232 to L-266; K-233 to L-266; L-234 to L-266; E-235 to L-266; E-236 to L-266; G-237 to L-266; D-238 to L-266; E-239 to L-266; L-240

to L-266; Q-241 to L-266; L-242 to L-266; A-243 to L-266; I-244 to L-266; P-245 to L-266; R-246 to L-266; E-247 to L-266; N-248 to L-266; A-249 to L-266; Q-250 to L-266; I-251 to L-266; S-252 to L-266; L-253 to L-266; D-254 to L-266; G-255 to L-266; D-256 to L-266; V-257 to L-266; T-258 to L-266; F-259 to L-266; F-260 to L-266; and G-261 to L-266 of SEQ ID NO:3229. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

[0139] Similarly, deletions of C-terminal amino acid residues of the predicted extracellular domain of BLyS up to the leucine residue at position 79 of SEQ ID NO:3229 may retain some functional activity, such as, for example, ligand binding, the ability to stimulate lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, modulation of cell replication, modulation of target cell activities and/or immunogenicity. Polypeptides having further C-terminal deletions including Leu-79 of SEQ ID NO:3229 would not be expected to retain biological activities.

[0140] However, even if deletion of one or more amino acids from the C-terminus of a polypeptide results in modification or loss of one or more functional activities (e.g., biological activity) of the polypeptide, other functional activities may still be retained. Thus, the ability of the shortened polypeptide to induce and/or bind to antibodies which recognize the complete, mature or extracellular forms of the polypeptide generally will be retained when less than the majority of the residues of the complete, mature or extracellular forms of the polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of the predicted extracellular domain retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

[0141] Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues from the carboxy terminus of the amino acid sequence of the predicted extracellular domain of BLyS shown in SEQ ID NO:3229, up to the leucine residue at position 79 of SEQ ID NO:3229. In particular, the present invention provides antibodies that bind polypeptides having the amino acid sequence of residues 73-m^4 of the amino acid sequence in SEQ ID NO:3229, where m^4 is any integer in the

range of the amino acid position of amino acid residues 79-265 of the amino acid sequence in SEQ ID NO:3229.

[0142] More in particular, in certain embodiments, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues Q-73 to L-265; Q-73 to K-264; Q-73 to L-263; Q-73 to A-262; Q-73 to G-261; Q-73 to F-260; Q-73 to F-259; Q-73 to T-258; Q-73 to V-257; Q-73 to D-256; Q-73 to G-255; Q-73 to D-254; Q-73 to L-253; Q-73 to S-252; Q-73 to I-251; Q-73 to Q-250; Q-73 to A-249; Q-73 to N-248; Q-73 to E-247; Q-73 to R-246; Q-73 to P-245; Q-73 to I-244; Q-73 to A-243; Q-73 to L-242; Q-73 to Q-241; Q-73 to L-240; Q-73 to E-239; Q-73 to D-238; Q-73 to G-237; Q-73 to E-236; Q-73 to E-235; Q-73 to L-234; Q-73 to K-233; Q-73 to A-232; Q-73 to I-231; Q-73 to G-230; Q-73 to A-229; Q-73 to S-228; Q-73 to Y-227; Q-73 to C-226; Q-73 to S-225; Q-73 to N-224; Q-73 to N-223; Q-73 to P-222; Q-73 to L-221; Q-73 to T-220; Q-73 to E-219; Q-73 to P-218; Q-73 to M-217; Q-73 to N-216; Q-73 to Q-215; Q-73 to I-214; Q-73 to C-213; Q-73 to R-212; Q-73 to F-211; Q-73 to L-210; Q-73 to T-209; Q-73 to V-208; Q-73 to L-207; Q-73 to S-206; Q-73 to L-205; Q-73 to E-204; Q-73 to D-203; Q-73 to G-202; Q-73 to F-201; Q-73 to V-200; Q-73 to H-199; Q-73 to V-198; Q-73 to K-197; Q-73 to K-196; Q-73 to R-195; Q-73 to Q-194; Q-73 to I-193; Q-73 to L-192; Q-73 to H-191; Q-73 to G-190; Q-73 to Q-7389; Q-73 to A-188; Q-73 to Y-187; Q-73 to T-186; Q-73 to K-185; Q-73 to D-184; Q-73 to T-183; Q-73 to Y-182; Q-73 to L-181; Q-73 to V-180; Q-73 to Q-179; Q-73 to G-178; Q-73 to Y-177; Q-73 to I-176; Q-73 to F-175; Q-73 to F-174; Q-73 to Y-173; Q-73 to G-172; Q-73 to T-171; Q-73 to E-170; Q-73 to K-169; Q-73 to V-168; Q-73 to L-167; Q-73 to I-166; Q-73 to K-165; Q-73 to N-164; Q-73 to E-163; Q-73 to K-162; Q-73 to E-161; Q-73 to E-160; Q-73 to L-159; Q-73 to A-158; Q-73 to S-157; Q-73 to G-156; Q-73 to R-155; Q-73 to K-154; Q-73 to F-153; Q-73 to S-152; Q-73 to L-151; Q-73 to L-150; Q-73 to W-149; Q-73 to P-148; Q-73 to V-147; Q-73 to F-146; Q-73 to T-145; Q-73 to Y-144; Q-73 to S-143; Q-73 to G-142; Q-73 to T-141; Q-73 to E-140; Q-73 to E-139; Q-73 to P-138; Q-73 to G-137; Q-73 to Q-136; Q-73 to V-135; Q-73 to A-134; Q-73 to R-133; Q-73 to K-132; Q-73 to N-131; Q-73 to R-130; Q-73 to S-129; Q-73 to N-128; Q-73 to Q-127; Q-73 to S-126; Q-73 to S-125; Q-73 to N-124; Q-73 to G-123; Q-73 to E-122; Q-73 to G-121; Q-73 to P-120; Q-73 to A-119; Q-73 to P-118; Q-73 to P-117; Q-73 to E-116; Q-73 to F-115;

Q-73 to I-114; Q-73 to K-113; Q-73 to L-112; Q-73 to G-111; Q-73 to A-110; Q-73 to T-109; Q-73 to V-108; Q-73 to A-107; Q-73 to P-106; Q-73 to A-105; Q-73 to E-104; Q-73 to E-103; Q-73 to L-102; Q-73 to G-101; Q-73 to A-100; Q-73 to K-99; Q-73 to P-98; Q-73 to A-97; Q-73 to G-96; Q-73 to A-95; Q-73 to G-94; Q-73 to A-93; Q-73 to P-92; Q-73 to L-91; Q-73 to K-90; Q-73 to E-89; Q-73 to A-88; Q-73 to H-87; Q-73 to H-86; Q-73 to G-85; Q-73 to Q-84; Q-73 to L-83; Q-73 to E-82; Q-73 to A-81; Q-73 to R-80; Q-73 to L-79; and Q-73 to S-78 of SEQ ID NO:3229. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

[0143] The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini of the predicted extracellular domain of BLyS, which may be described generally as having residues n^4-m^4 of SEQ ID NO:3229 where n^4 and m^4 are integers as defined above.

[0144] In another embodiment, antibodies of the present invention bind polypeptides consisting of a portion of the extracellular domain of the BLyS amino acid sequence encoded by the cDNA clone contained in the deposit having ATCC Accession No. 203518, where this portion excludes from 1 to about 260 amino acids from the amino terminus of the extracellular domain of the amino acid sequence encoded by cDNA clone contained in the deposit having ATCC Accession No. 203518, or from 1 to about 187 amino acids from the carboxy terminus of the extracellular domain of the amino acid sequence encoded by cDNA clone contained in the deposit having ATCC Accession No. 203518, or any combination of the above amino terminal and carboxy terminal deletions, of the entire extracellular domain of the amino acid sequence encoded by the cDNA clone contained in the deposit having ATCC Aecession No. 203518.

[0145] As mentioned above, even if deletion of one or more amino acids from the N-terminus of a polypeptide results in modification or loss of one or more functional activities (e.g., biological activity) of the polypeptide, other functional activities may still be retained. Thus, the ability of a shortened BLyS polypeptide to induce and/or bind to antibodies which recognize the full-length or mature forms or the extracellular domain of the polypeptide generally will be retained when less than the majority of the residues of

the full-length or mature or extracellular domain of the polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a BLyS mutein with a large number of deleted N-terminal amino acid residues may retain functional (e.g., immunogenic) activities. In faet, peptides composed of as few as six BLyS amino acid residues may often evoke an immune response.

[0146] Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the predicted full-length amino acid sequence of the BLyS polypeptide shown in SEQ ID NO:3229, up to the glycine residue at position number 261 of the sequence shown SEQ ID NO:3229 and polynucleotides encoding such polypeptides. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues n^5-266 of the sequence shown in SEQ ID NO:3229, where n^5 is an integer in the range of the amino acid position of amino acid residues 1 to 261 of the amino acid sequence in SEQ ID NO:3229.

[0147] More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues of D-2 to L-266; D-3 to L-266; S-4 to L-266; T-5 to L-266; E-6 to L-266; R-7 to L-266; E-8 to L-266; Q-9 to L-266; S-10 to L-266; R-11 to L-266; L-12 to L-266; T-13 to L-266; S-14 to L-266; C-15 to L-266; L-16 to L-266; K-17 to L-266; K-18 to L-266; R-19 to L-266; E-20 to L-266; E-21 to L-266; M-22 to L-266; K-23 to L-266; L-24 to L-266; K-25 to L-266; E-26 to L-266; C-27 to L-266; V-28 to L-266; S-29 to L-266; I-30 to L-266; L-31 to L-266; P-32 to L-266; R-33 to L-266; K-34 to L-266; E-35 to L-266; S-36 to L-266; P-37 to L-266; S-38 to L-266; V-39 to L-266; R-40 to L-266; S-41 to L-266; S-42 to L-266; K-43 to L-266; D-44 to L-266; G-45 to L-266; K-46 to L-266; L-47 to L-266; L-48 to L-266; A-49 to L-266; A-50 to L-266; T-51 to L-266; L-52 to L-266; L-53 to L-266; L-54 to L-266; A-55 to L-266; L-56 to L-266; L-57 to L-266; S-58 to L-266; C-59 to L-266; C-60 to L-266; L-61 to L-266; T-62 to L-266; V-63 to L-266; V-64 to L-266; S-65 to L-266; F-66 to L-266; Y-67 to L-266; Q-68 to L-266; V-69 to L-266; A-70 to L-266; A-71 to L-266; L-72 to L-266; Q-73 to L-266; G-74 to L-266; D-75 to L-266; L-76 to L-266; A-77 to L-266; S-78 to L-266; L-79 to L-266; R-80 to

L-266; A-81 to L-266; E-82 to L-266; L-83 to L-266; Q-84 to L-266; G-85 to L-266; H-86 to L-266; H-87 to L-266; A-88 to L-266; E-89 to L-266; K-90 to L-266; L-91 to L-266; P-92 to L-266; A-93 to L-266; G-94 to L-266; A-95 to L-266; G-96 to L-266; A-97 to L-266; P-98 to L-266; K-99 to L-266; A-100 to L-266; G-101 to L-266; L-102 to L-266; E-103 to L-266; E-104 to L-266; A-105 to L-266; P-106 to L-266; A-107 to L-266; V-108 to L-266; T-109 to L-266; A-110 to L-266; G-111 to L-266; L-112 to L-266; K-113 to L-266; I-114 to L-266; F-115 to L-266; E-116 to L-266; P-117 to L-266; P-118 to L-266; A-119 to L-266; P-120 to L-266; G-121 to L-266; E-122 to L-266; G-123 to L-266; N-124 to L-266; S-125 to L-266; S-126 to L-266; Q-127 to L-266; N-128 to L-266; S-129 to L-266; R-130 to L-266; N-131 to L-266; K-132 to L-266; R-133 to L-266; A-134 to L-266; V-135 to L-266; Q-136 to L-266; G-137 to L-266; P-138 to L-266; E-139 to L-266; E-140 to L-266; T-141 to L-266; G-142 to L-266; S-143 to L-266; Y-144 to L-266; T-145 to L-266; F-146 to L-266; V-147 to L-266; P-148 to L-266; W-149 to L-266; L-150 to L-266; L-151 to L-266; S-152 to L-266; F-153 to L-266; K-154 to L-266; R-155 to L-266; G-156 to L-266; S-157 to L-266; A-158 to L-266; L-159 to L-266; E-160 to L-266; E-161 to L-266; K-162 to L-266; E-163 to L-266; N-164 to L-266; K-165 to L-266; I-166 to L-266; L-167 to L-266; V-168 to L-266; K-169 to L-266; E-170 to L-266; T-171 to L-266; G-172 to L-266; Y-173 to L-266; F-174 to L-266; F-175 to L-266; I-176 to L-266; Y-177 to L-266; G-178 to L-266; Q-179 to L-266; V-180 to L-266; L-181 to L-266; Y-182 to L-266; T-183 to L-266; D-184 to L-266; K-185 to L-266; T-186 to L-266; Y-187 to L-266; A-188 to L-266; M-189 to L-266; G-190 to L-266; H-191 to L-266; L-192 to L-266; I-193 to L-266; Q-194 to L-266; R-195 to L-266; K-196 to L-266; K-197 to L-266; V-198 to L-266; H-199 to L-266; V-200 to L-266; F-201 to L-266; G-202 to L-266; D-203 to L-266; E-204 to L-266; L-205 to L-266; S-206 to L-266; L-207 to L-266; V-208 to L-266; T-209 to L-266; L-210 to L-266; F-211 to L-266; R-212 to L-266; C-213 to L-266; I-214 to L-266; Q-215 to L-266; N-216 to L-266; M-217 to L-266; P-218 to L-266; E-219 to L-266; T-220 to L-266; L-221 to L-266; P-222 to L-266; N-223 to L-266; N-224 to L-266; S-225 to L-266; C-226 to L-266; Y-227 to L-266; S-228 to L-266; A-229 to L-266; G-230 to L-266; I-231 to L-266; A-232 to L-266; K-233 to L-266; L-234 to L-266; E-235 to L-266; E-236 to L-266; G-237 to L-266; D-238 to L-266; E-239 to L-266; L-240 to L-266; Q-241 to L-266; L-242 to L-266; A-243 to L-266; I-244 to L-266; P-245 to L-266; R-246 to L-266; E-247 to L-266; N-248 to L-266; A-249 to L-266; Q-250 to

L-266; I-251 to L-266; S-252 to L-266; L-253 to L-266; D-254 to L-266; G-255 to L-266; D-256 to L-266; V-257 to L-266; T-258 to L-266; F-259 to L-266; F-260 to L-266; and G-261 to L-266 of SEQ ID NO:3229. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

[0148] Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more functional activities (e.g., biological activities) of the protein, other functional activities may still be retained. Thus, the ability of a shortened BLyS mutein to induce and/or bind to antibodies which recognize the complete or mature form or the extracellular domain of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature form or the extracellular domain of the polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a BLyS mutein with a large number of deleted C-terminal amino acid residues may retain some functional (e.g., immunogenic) activities. In fact, peptides composed of as few as six BLyS amino acid residues may often evoke an immune response.

[0149] Accordingly, the present invention further provides in another embodiment, antibodies that bind polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the BLyS shown in SEQ ID NO:3229, up to the glutamic acid residue at position number 6, and polynucleotides encoding such polypeptides. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues 1-m^5 of SEQ ID NO:3229, where m^5 is an integer in the range of the amino acid position of amino acid residues 6 to 265 in the amino acid sequence of SEQ ID NO:3229.

[0150] More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues M-1 to L-265; M-1 to K-264; M-1 to L-263; M-1 to A-262; M-1 to G-261; M-1 to F-260; M-1 to F-259; M-1 to T-258; M-1 to V-257; M-1 to D-256; M-1 to G-255; M-1 to D-254; M-1 to L-253; M-1 to S-252; M-1 to I-251; M-1 to Q-250; M-1 to

A-249; M-1 to N-248; M-1 to E-247; M-1 to R-246; M-1 to P-245; M-1 to I-244; M-1 to A-243; M-1 to L-242; M-1 to Q-241; M-1 to L-240; M-1 to E-239; M-1 to D-238; M-1 to G-237; M-1 to E-236; M-1 to E-235; M-1 to L-234; M-1 to K-233; M-1 to A-232; M-1 to I-231; M-1 to G-230; M-1 to A-229; M-1 to S-228; M-1 to Y-227; M-1 to C-226; M-1 to S-225; M-1 to N-224; M-1 to N-223; M-1 to P-222; M-1 to L-221; M-1 to T-220; M-1 to E-219; M-1 to P-218; M-1 to M-217; M-1 to N-216; M-1 to Q-215; M-1 to I-214; M-1 to C-213; M-1 to R-212; M-1 to F-211; M-1 to L-210; M-1 to T-209; M-1 to V-208; M-1 to L-207; M-1 to S-206; M-1 to L-205; M-1 to E-204; M-1 to D-203; M-1 to G-202; M-1 to F-201; M-1 to V-200; M-1 to H-199; M-1 to V-198; M-1 to K-197; M-1 to K-196; M-1 to R-195; M-1 to Q-194; M-1 to I-193; M-1 to L-192; M-1 to H-191; M-1 to G-190; M-1 to M-189; M-1 to A-188; M-1 to Y-187; M-1 to T-186; M-1 to K-185; M-1 to D-184; M-1 to T-183; M-1 to Y-182; M-1 to L-181; M-1 to V-180; M-1 to Q-179; M-1 to G-178; M-1 to Y-177; M-1 to I-176; M-1 to F-175; M-1 to F-174; M-1 to Y-173; M-1 to G-172; M-1 to T-171; M-1 to E-170; M-1 to K-169; M-1 to V-168; M-1 to L-167; M-1 to I-166; M-1 to K-165; M-1 to N-164; M-1 to E-163; M-1 to K-162; M-1 to E-161; M-1 to E-160; M-1 to L-159; M-1 to A-158; M-1 to S-157; M-1 to G-156; M-1 to R-155; M-1 to K-154; M-1 to F-153; M-1 to S-152; M-1 to L-151; M-1 to L-150; M-1 to W-149; M-1 to P-148; M-1 to V-147; M-1 to F-146; M-1 to T-145; M-1 to Y-144; M-1 to S-143; M-1 to G-142; M-1 to T-141; M-1 to E-140; M-1 to E-139; M-1 to P-138; M-1 to G-137; M-1 to Q-136; M-1 to V-135; M-1 to A-134; M-1 to R-133; M-1 to K-132; M-1 to N-131; M-1 to R-130; M-1 to S-129; M-1 to N-128; M-1 to Q-127; M-1 to S-126; M-1 to S-125; M-1 to N-124; M-1 to G-123; M-1 to E-122; M-1 to G-121; M-1 to P-120; M-1 to A-119; M-1 to P-118; M-1 to P-117; M-1 to E-116; M-1 to F-115; M-1 to I-114; M-1 to K-113; M-1 to L-112; M-1 to G-111; M-1 to A-110; M-1 to T-109; M-1 to V-108; M-1 to A-107; M-1 to P-106; M-1 to A-105; M-1 to E-104; M-1 to E-103; M-1 to L-102; M-1 to G-101; M-1 to A-100; M-1 to K-99; M-1 to P-98; M-1 to A-97; M-1 to G-96; M-1 to A-95; M-1 to G-94; M-1 to A-93; M-1 to P-92; M-1 to L-91; M-1 to K-90; M-1 to E-89; M-1 to A-88; M-1 to H-87; M-1 to H-86; M-1 to G-85; M-1 to Q-84; M-1 to L-83; M-1 to E-82; M-1 to A-81; M-1 to R-80; M-1 to L-79; M-1 to S-78; M-1 to A-77; M-1 to L-76; M-1 to D-75; M-1 to G-74; M-1 to Q-73; M-1 to L-72; M-1 to A-71; M-1 to A-70; M-1 to V-69; M-1 to Q-68; M-1 to Y-67; M-1 to F-66; M-1 to S-65; M-1 to V-64; M-1 to V-63; M-1 to T-62; M-1 to L-61; M-1 to C-60; M-1 to C-59; M-1 to S-58; M-1 to L-57; M-1 to L-56; M-1 to A-55; M-1 to L-54;

M-1 to L-53; M-1 to L-52; M-1 to T-51; M-1 to A-50; M-1 to A-49; M-1 to L-48; M-1 to L-47; M-1 to K-46; M-1 to G-45; M-1 to D-44; M-1 to K-43; M-1 to S-42; M-1 to S-41; M-1 to R-40; M-1 to V-39; M-1 to S-38; M-1 to P-37; M-1 to S-36; M-1 to E-35; M-1 to K-34; M-1 to R-33; M-1 to P-32; M-1 to L-31; M-1 to I-30; M-1 to S-29; M-1 to V-28; M-1 to C-27; M-1 to E-26; M-1 to K-25; M-1 to L-24; M-1 to K-23; M-1 to M-22; M-1 to E-21; M-1 to E-20; M-1 to R-19; M-1 to K-18; M-1 to K-17; M-1 to L-16; M-1 to C-15; M-1 to S-14; M-1 to T-13; M-1 to L-12; M-1 to R-11; M-1 to S-10; M-1 to Q-9; M-1 to E-8; M-1 to R-7; and M-1 to E-6 of SEQ ID NO:3229. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

[0151] The invention also provides antibodies that bind polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini of a BLyS polypeptide, which may be described generally as having residues n^5-m^5 of SEQ ID NO:3229, where n^5 and m^5 are integers as defined above.

[0152] In additional embodiments, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues 134-m^6 of SEQ ID NO:3228, where m^6 is an integer from 140 to 285, corresponding to the position of the amino acid residue in SEQ ID NO:3228. For example, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues A-134 to Leu-285; A-134 to L-284; A-134 to K-283; A-134 to L-282; A-134 to A-281; A-134 to G-280; A-134 to F-279; A-134 to F-278; A-134 to T-277; A-134 to V-276; A-134 to D-275; A-134 to G-274; A-134 to D-273; A-134 to L-272; A-134 to S-271; A-134 to I-270; A-134 to Q-269; A-134 to A-268; A-134 to N-267; A-134 to E-266; A-134 to R-265; A-134 to P-264; A-134 to I-263; A-134 to A-262; A-134 to L-261; A-134 to Q-260; A-134 to L-259; A-134 to E-258; A-134 to D-257; A-134 to G-256; A-134 to E-255; A-134 to E-254; A-134 to L-253; A-134 to K-252; A-134 to A-251; A-134 to I-250; A-134 to G-249; A-134 to A-248; A-134 to S-247; A-134 to Y-246; A-134 to C-245; A-134 to S-244; A-134 to N-243; A-134 to N-242; A-134 to P-241; A-134 to L-240; A-134 to T-239; A-134 to E-238; A-134 to P-237; A-134 to M-236; A-134 to N-235; A-134 to Q-234; A-134 to

I-233; A-134 to C-232; A-134 to R-231; A-134 to F-230; A-134 to L-229; A-134 to T-228; A-134 to V-227; A-134 to L-226; A-134 to S-225; A-134 to L-224; A-134 to E-223; A-134 to D-222; A-134 to G-221; A-134 to F-220; A-134 to V-219; A-134 to H-218; A-134 to V-217; A-134 to K-216; A-134 to K-215; A-134 to R-214; A-134 to Q-213; A-134 to I-212; A-134 to L-211; A-134 to H-210; A-134 to G-209; A-134 to M-208; A-134 to A-207; A-134 to Y-206; A-134 to T-205; A-134 to K-204; A-134 to D-203; A-134 to T-202; A-134 to Y-201; A-134 to L-200; A-134 to V-199; A-134 to Q-198; A-134 to G-197; A-134 to Y-196; A-134 to I-195; A-134 to F-194; A-134 to F-193; A-134 to Y-192; A-134 to G-191; A-134 to T-190; A-134 to E-189; A-134 to K-188; A-134 to V-187; A-134 to L-186; A-134 to I-185; A-134 to K-184; A-134 to N-183; A-134 to E-182; A-134 to K-181; A-134 to E-180; A-134 to E-179; A-134 to L-178; A-134 to A-177; A-134 to S-176; A-134 to G-175; A-134 to R-174; A-134 to K-173; A-134 to F-172; A-134 to S-171; A-134 to L-170; A-134 to L-169; A-134 to W-168; A-134 to P-167; A-134 to V-166; A-134 to F-165; A-134 to T-164; A-134 to Y-163; A-134 to S-162; A-134 to G-161; A-134 to K-160; A-134 to Q-159; A-134 to I-158; A-134 to T-157; A-134 to P-156; A-134 to T-155; A-134 to E-154; A-134 to S-153; A-134 to D-152; A-134 to A-151; A-134 to I-150; A-134 to L-149; A-134 to Q-148; A-134 to L-147; A-134 to C-146; A-134 to D-145; A-134 to Q-144; A-134 to T-143; A-134 to V-142; A-134 to T-141; and A-134 to E-140 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

[0153] In additional embodiments, antibodies of the present invention may bind polypeptide fragments comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues: M-1 to C-15; D-2 to L-16; D-3 to K-17; S-4 to K-18; T-5 to R-19; E-6 to E-20; R-7 to E-21; E-8 to M-22; Q-9 to K-23; S-10 to L-24; R-11 to K-25; L-12 to E-26; T-13 to C-27; S-14 to V-28; C-15 to S-29; L-16 to I-30; K-17 to L-31; K-18 to P-32; R-19 to R-33; E-20 to K-34; E-21 to E-35; M-22 to S-36; K-23 to P-37; L-24 to S-38; K-25 to V-39; E-26 to R-40; C-27 to S-41; V-28 to S-42; S-29 to K-43; I-30 to D-44; L-31 to G-45; P-32 to K-46; R-33 to L-47; K-34 to L-48; E-35 to A-49; S-36 to A-50; P-37 to T-51; S-38 to L-52; V-39 to L-53; R-40 to L-54; S-41 to A-55; S-42

to L-56; K-43 to L-57; D-44 to S-58; G-45 to C-59; K-46 to C-60; L-47 to L-61; L-48 to T-62; A-49 to V-63; A-50 to V-64; T-51 to S-65; L-52 to F-66; L-53 to Y-67; L-54 to Q-68; A-55 to V-69; L-56 to A-70; L-57 to A-71; S-58 to L-72; C-59 to Q-73; C-60 to G-74; L-61 to D-75; T-62 to L-76; V-63 to A-77; V-64 to S-78; S-65 to L-79; F-66 to R-80; Y-67 to A-81; Q-68 to E-82; V-69 to L-83; A-70 to Q-84; A-71 to G-85; L-72 to H-86; Q-73 to H-87; G-74 to A-88; D-75 to E-89; L-76 to K-90; A-77 to L-91; S-78 to P-92; L-79 to A-93; R-80 to G-94; A-81 to A-95; E-82 to G-96; L-83 to A-97; Q-84 to P-98; G-85 to K-99; H-86 to A-100; H-87 to G-101; A-88 to L-102; E-89 to E-103; K-90 to E-104; L-91 to A-105; P-92 to P-106; A-93 to A-107; G-94 to V-108; A-95 to T-109; G-96 to A-110; A-97 to G-111; P-98 to L-112; K-99 to K-113; A-100 to I-114; G-101 to F-115; L-102 to E-116; E-103 to P-117; E-104 to P-118; A-105 to A-119; P-106 to P-120; A-107 to G-121; V-108 to E-122; T-109 to G-123; A-110 to N-124; G-111 to S-125; L-112 to S-126; K-113 to Q-127; I-114 to N-128; F-115 to S-129; E-116 to R-130; P-117 to N-131; P-118 to K-132; A-119 to R-133; P-120 to A-134; G-121 to V-135; E-122 to Q-136; G-123 to G-137; N-124 to P-138; S-125 to E-139; S-126 to E-140; Q-127 to T-141; N-128 to V-142; S-129 to T-143; R-130 to Q-144; N-131 to D-145; K-132 to C-146; R-133 to L-147; A-134 to Q-148; V-135 to L-149; Q-136 to I-150; G-137 to A-151; P-138 to D-152; E-139 to S-153; E-140 to E-154; T-141 to T-155; V-142 to P-156; T-143 to T-157; Q-144 to I-158; D-145 to Q-159; C-146 to K-160; L-147 to G-161; Q-148 to S-162; L-149 to Y-163; I-150 to T-164; A-151 to F-165; D-152 to V-166; S-153 to P-167; E-154 to W-168; T-155 to L-169; P-156 to L-170; T-157 to S-171; I-158 to F-172; Q-159 to K-173; K-160 to R-174; G-161 to G-175; S-162 to S-176; Y-163 to A-177; T-164 to L-178; F-165 to E-179; V-166 to E-180; P-167 to K-181; W-168 to E-182; L-169 to N-183; L-170 to K-184; S-171 to I-185; F-172 to L-186; K-173 to V-187; R-174 to K-188; G-175 to E-189; S-176 to T-190; A-177 to G-191; L-178 to Y-192; E-179 to F-193; E-180 to F-194; K-181 to I-195; E-182 to Y-196; N-183 to G-197; K-184 to Q-198; I-185 to V-199; L-186 to L-200; V-187 to Y-201; K-188 to T-202; E-189 to D-203; T-190 to K-204; G-191 to T-205; Y-192 to Y-206; F-193 to A-207; F-194 to M-208; I-195 to G-209; Y-196 to H-210; G-197 to L-211; Q-198 to I-212; V-199 to Q-213; L-200 to R-214; Y-201 to K-215; T-202 to K-216; D-203 to V-217; K-204 to H-218; T-205 to V-219; Y-206 to F-220; A-207 to G-221; M-208 to D-222; G-209 to E-223; H-210 to L-224; L-211 to S-225; I-212 to L-226; Q-213 to V-227; R-214 to T-228; K-215 to L-229; K-216 to F-230; V-217 to R-231; H-218 to C-232;

V-219 to I-233; F-220 to Q-234; G-221 to N-235; D-222 to M-236; E-223 to P-237; L-224 to E-238; S-225 to T-239; L-226 to L-240; V-227 to P-241; T-228 to N-242; L-229 to N-243; F-230 to S-244; R-231 to C-245; C-232 to Y-246; I-233 to S-247; Q-234 to A-248; N-235 to G-249; M-236 to I-250; P-237 to A-251; E-238 to K-252; T-239 to L-253; L-240 to E-254; P-241 to E-255; N-242 to G-256; N-243 to D-257; S-244 to E-258; C-245 to L-259; Y-246 to Q-260; S-247 to L-261; A-248 to A-262; G-249 to I-263; I-250 to P-264; A-251 to R-265; K-252 to E-266; L-253 to N-267; E-254 to A-268; E-255 to Q-269; G-256 to I-270; D-257 to S-271; E-258 to L-272; L-259 to D-273; Q-260 to G-274; L-261 to D-275; A-262 to V-276; I-263 to T-277; P-264 to F-278; R-265 to F-279; E-266 to G-280; N-267 to A-281; A-268 to L-282; Q-269 to K-283; I-270 to L-284; and S-271 to L-285 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

[0154] In additional embodiments, antibodies of the present invention may bind polypeptide fragments comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues: M-1 to C-15; D-2 to L-16; D-3 to K-17; S-4 to K-18; T-5 to R-19; E-6 to E-20; R-7 to E-21; E-8 to M-22; Q-9 to K-23; S-10 to L-24; R-11 to K-25; L-12 to E-26; T-13 to C-27; S-14 to V-28; C-15 to S-29; L-16 to I-30; K-17 to L-31; K-18 to P-32; R-19 to R-33; E-20 to K-34; E-21 to E-35; M-22 to S-36; K-23 to P-37; L-24 to S-38; K-25 to V-39; E-26 to R-40; C-27 to S-41; V-28 to S-42; S-29 to K-43; I-30 to D-44; L-31 to G-45; P-32 to K-46; R-33 to L-47; K-34 to L-48; E-35 to A-49; S-36 to A-50; P-37 to T-51; S-38 to L-52; V-39 to L-53; R-40 to L-54; S-41 to A-55; S-42 to L-56; K-43 to L-57; D-44 to S-58; G-45 to C-59; K-46 to C-60; L-47 to L-61; L-48 to T-62; A-49 to V-63; A-50 to V-64; T-51 to S-65; L-52 to F-66; L-53 to Y-67; L-54 to Q-68; A-55 to V-69; L-56 to A-70; L-57 to A-71; S-58 to L-72; C-59 to Q-73; C-60 to G-74; L-61 to D-75; T-62 to L-76; V-63 to A-77; V-64 to S-78; S-65 to L-79; F-66 to R-80; Y-67 to A-81; Q-68 to E-82; V-69 to L-83; A-70 to Q-84; A-71 to G-85; L-72 to H-86; Q-73 to H-87; G-74 to A-88; D-75 to E-89; L-76 to K-90; A-77 to L-91; S-78 to P-92; L-79 to A-93; R-80 to G-94; A-81 to A-95; E-82 to G-96; L-83 to A-97; Q-84 to P-98; G-85 to K-99; H-86 to A-100; H-87 to G-101; A-88 to L-102; E-89 to E-103; K-90 to E-104; L-91 to A-105; P-92 to P-106; A-93 to A-107; G-94 to V-108; A-95 to T-109; G-96 to A-110; A-

97 to G-111; P-98 to L-112; K-99 to K-113; A-100 to I-114; G-101 to F-115; L-102 to E-116; E-103 to P-117; E-104 to P-118; A-105 to A-119; P-106 to P-120; A-107 to G-121; V-108 to E-122; T-109 to G-123; A-110 to N-124; G-111 to S-125; L-112 to S-126; K-113 to Q-127; I-114 to N-128; F-115 to S-129; E-116 to R-130; P-117 to N-131; P-118 to K-132; A-119 to R-133; P-120 to A-134; G-121 to V-135; E-122 to Q-136; G-123 to G-137; N-124 to P-138; S-125 to E-139; S-126 to E-140; Q-127 to T-141; N-128 to G-142; S-129 to S-143; R-130 to Y-144; N-131 to T-145; K-132 to F-146; R-133 to V-147; A-134 to P-148; V-135 to W-149; Q-136 to L-150; G-137 to L-151; P-138 to S-152; E-139 to F-153; E-140 to K-154; T-141 to R-155; G-142 to G-156; S-143 to S-157; Y-144 to A-158; T-145 to L-159; F-146 to E-160; V-147 to E-161; P-148 to K-162; W-149 to E-163; L-150 to N-164; L-151 to K-165; S-152 to I-166; F-153 to L-167; K-154 to V-168; R-155 to K-169; G-156 to E-170; S-157 to T-171; A-158 to G-172; L-159 to Y-173; E-160 to F-174; E-161 to F-175; K-162 to I-176; E-163 to Y-177; N-164 to G-178; K-165 to Q-179; I-166 to V-180; L-167 to L-181; V-168 to Y-182; K-169 to T-183; E-170 to D-184; T-171 to K-185; G-172 to T-186; Y-173 to Y-187; F-174 to A-188; F-175 to M-189; I-176 to G-190; Y-177 to H-191; G-178 to L-192; Q-179 to I-193; V-180 to Q-194; L-181 to R-195; Y-182 to K-196; T-183 to K-197; D-184 to V-198; K-185 to H-199; T-186 to V-200; Y-187 to F-201; A-188 to G-202; M-189 to D-203; G-190 to E-204; H-191 to L-205; L-192 to S-206; I-193 to L-207; Q-194 to V-208; R-195 to T-209; K-196 to L-210; K-197 to F-211; V-198 to R-212; H-199 to C-213; V-200 to I-214; F-201 to Q-215; G-202 to N-216; D-203 to M-217; E-204 to P-218; L-205 to E-219; S-206 to T-220; L-207 to L-221; V-208 to P-222; T-209 to N-223; L-210 to N-224; F-211 to S-225; R-212 to C-226; C-213 to Y-227; I-214 to S-228; Q-215 to A-229; N-216 to G-230; M-217 to I-231; P-218 to A-232; E-219 to K-233; T-220 to L-234; L-221 to E-235; P-222 to E-236; N-223 to G-237; N-224 to D-238; S-225 to E-239; C-226 to L-240; Y-227 to Q-241; S-228 to L-242; A-229 to A-243; G-230 to I-244; I-231 to P-245; A-232 to R-246; K-233 to E-247; L-234 to N-248; E-235 to A-249; E-236 to Q-250; G-237 to I-251; D-238 to S-252; E-239 to L-253; L-240 to D-254; Q-241 to G-255; L-242 to D-256; A-243 to V-257; I-244 to T-258; P-245 to F-259; R-246 to F-260; E-247 to G-261; N-248 to A-262; A-249 to L-263; Q-250 to K-264; I-251 to L-265; and S-252 to L-266 of SEQ ID NO:3229. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%,

96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

[0155] In additional embodiments, antibodies of the present invention may bind polypeptide fragments comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues: M-1 to F-15; D-2 to C-16; E-3 to S-17; S-4 to E-18; A-5 to K-19; K-6 to G-20; T-7 to E-21; L-8 to D-22; P-9 to M-23; P-10 to K-24; P-11 to V-25; C-12 to G-26; L-13 to Y-27; C-14 to D-28; F-15 to P-29; C-16 to I-30; S-17 to T-31; E-18 to P-32; K-19 to Q-33; G-20 to K-34; E-21 to E-35; D-22 to E-36; M-23 to G-37; K-24 to A-38; V-25 to W-39; G-26 to F-40; Y-27 to G-41; D-28 to I-42; P-29 to C-43; I-30 to R-44; T-31 to D-45; P-32 to G-46; Q-33 to R-47; K-34 to L-48; E-35 to L-49; E-36 to A-50; G-37 to A-51; A-38 to T-52; W-39 to L-53; F-40 to L-54; G-41 to L-55; I-42 to A-56; C-43 to L-57; R-44 to L-58; D-45 to S-59; G-46 to S-60; R-47 to S-61; L-48 to F-62; L-49 to T-63; A-50 to A-64; A-51 to M-65; T-52 to S-66; L-53 to L-67; L-54 to Y-68; L-55 to Q-69; A-56 to L-70; L-57 to A-71; L-58 to A-72; S-59 to L-73; S-60 to Q-74; S-61 to A-75; F-62 to D-76; T-63 to L-77; A-64 to M-78; M-65 to N-79; S-66 to L-80; L-67 to R-81; Y-68 to M-82; Q-69 to E-83; L-70 to L-84; A-71 to Q-85; A-72 to S-86; L-73 to Y-87; Q-74 to R-88; A-75 to G-89; D-76 to S-90; L-77 to A-91; M-78 to T-92; N-79 to P-93; L-80 to A-94; R-81 to A-95; M-82 to A-96; E-83 to G-97; L-84 to A-98; Q-85 to P-99; S-86 to E-100; Y-87 to L-101; R-88 to T-102; G-89 to A-103; S-90 to G-104; A-91 to V-105; T-92 to K-106; P-93 to L-107; A-94 to L-108; A-95 to T-109; A-96 to P-110; G-97 to A-111; A-98 to A-112; P-99 to P-113; E-100 to R-114; L-101 to P-115; T-102 to H-116; A-103 to N-117; G-104 to S-118; V-105 to S-119; K-106 to R-120; L-107 to G-121; L-108 to H-122; T-109 to R-123; P-110 to N-124; A-111 to R-125; A-112 to R-126; P-113 to A-127; R-114 to F-128; P-115 to Q-129; H-116 to G-130; N-117 to P-131; S-118 to E-132; S-119 to E-133; R-120 to T-134; G-121 to E-135; H-122 to Q-136; R-123 to D-137; N-124 to V-138; R-125 to D-139; R-126 to L-140; A-127 to S-141; F-128 to A-142; Q-129 to P-143; G-130 to P-144; P-131 to A-145; E-132 to P-146; E-133 to C-147; T-134 to L-148; E-135 to P-149; Q-136 to G-150; D-137 to C-151; V-138 to R-152; D-139 to H-153; L-140 to S-154; S-141 to Q-155; A-142 to H-156; P-143 to D-157; P-144 to D-158; A-145 to N-159; P-146 to G-160; C-147 to M-161; L-148 to N-162; P-149 to L-163; G-150 to R-164; C-151 to N-165; R-152 to I-166; H-153 to I-167; S-154 to Q-168; Q-155 to D-169; H-156 to C-170; D-157 to L-171; D-158 to Q-172; N-159 to L-173; G-160 to I-

174; M-161 to A-175; N-162 to D-176; L-163 to S-177; R-164 to D-178; N-165 to T-179; I-166 to P-180; I-167 to A-181; Q-168 to L-182; D-169 to E-183; C-170 to E-184; L-171 to K-185; Q-172 to E-186; L-173 to N-187; I-174 to K-188; A-175 to I-189; D-176 to V-190; S-177 to V-191; D-178 to R-192; T-179 to Q-193; P-180 to T-194; A-181 to G-195; L-182 to Y-196; E-183 to F-197; E-184 to F-198; K-185 to I-199; E-186 to Y-200; N-187 to S-201; K-188 to Q-202; I-189 to V-203; V-190 to L-204; V-191 to Y-205; R-192 to T-206; Q-193 to D-207; T-194 to P-208; G-195 to I-209; Y-196 to F-210; F-197 to A-211; F-198 to M-212; I-199 to G-213; Y-200 to H-214; S-201 to V-215; Q-202 to I-216; V-203 to Q-217; L-204 to R-218; Y-205 to K-219; T-206 to K-220; D-207 to V-221; P-208 to H-222; I-209 to V-223; F-210 to F-224; A-211 to G-225; M-212 to D-226; G-213 to E-227; H-214 to L-228; V-215 to S-229; I-216 to L-230; Q-217 to V-231; R-218 to T-232; K-219 to L-233; K-220 to F-234; V-221 to R-235; H-222 to C-236; V-223 to I-237; F-224 to Q-238; G-225 to N-239; D-226 to M-240; E-227 to P-241; L-228 to K-242; S-229 to T-243; L-230 to L-244; V-231 to P-245; T-232 to N-246; L-233 to N-247; F-234 to S-248; R-235 to C-249; C-236 to Y-250; I-237 to S-251; Q-238 to A-252; N-239 to G-253; M-240 to I-254; P-241 to A-255; K-242 to R-256; T-243 to L-257; L-244 to E-258; P-245 to E-259; N-246 to G-260; N-247 to D-261; S-248 to E-262; C-249 to I-263; Y-250 to Q-264; S-251 to L-265; A-252 to A-266; G-253 to I-267; I-254 to P-268; A-255 to R-269; R-256 to E-270; L-257 to N-271; E-258 to A-272; E-259 to Q-273; G-260 to I-274; D-261 to S-275; E-262 to R-276; I-263 to N-277; Q-264 to G-278; L-265 to D-279; A-266 to D-280; I-267 to T-281; P-268 to F-282; R-269 to F-283; E-270 to G-284; N-271 to A-285; A-272 to L-286; Q-273 to K-287; I-274 to L-288; and S-275 to L-289 of SEQ ID NO:38. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

[0156] It will be recognized by one of ordinary skill in the art that some amino acid sequences of the BLyS polypeptides can be varied without significant effect of the structure or function of the polypeptide. If such differences in sequence are contemplated, it should be remembered that there will be critical areas on the polypeptide which determine activity.

[0157] Thus, the invention further includes antibodies that bind variations of BLyS polypeptides which show BLyS polypeptide functional activity (e.g., biological aetivity) or which include regions of BLyS polypeptide such as the polypeptide fragments described herein. Such mutants include deletions, insertions, inversions, repeats, and type substitutions selected according to general rules known in the art so as have little effect on activity. For example, guidance coneerning how to make phenotypically silent amino acid substitutions is provided in Bowie, J. U. et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," *Science 247*:1306-1310 (1990), wherein the authors indieate that there are two main approaches for studying the tolerance of an amino acid sequence to change. The first method relies on the process of evolution, in which mutations are either accepted or rejected by natural selection. The second approach uses genetic engineering to introduee amino acid changes at specific positions of a cloned gene and selections or screens to identify sequences that maintain functionality.

[0158] As the authors state, these studies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at a eertain position of the protein. For example, most buried amino acid residues require nonpolar side ehains, whereas few features of surface side chains are generally conserved. Other such phenotypically silent substitutions are described in Bowie, J. U. *et al., supra*, and the references cited therein. Typically seen as conservative substitutions are the replacements, one for another, among the aliphatic amino acids Ala, Val, Leu and Ile; interchange of the hydroxyl residues Ser and Thr, exchange of the acidic residues Asp and Glu, substitution between the amide residues Asn and Gln, exchange of the basic residues Lys and Arg and replacements among the aromatic residues Phe, Tyr.

[0159] Thus, antibodies of the present invention may bind fragments, derivatives or analogs of the polypeptide of SEQ ID NO:3228, or that encoded by the deposited cDNA plasmid, such as (i) polypeptides in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino aeid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code, or (ii) polypeptides in which one or more of the amino acid residues includes a substituent group, or (iii) polypeptides in which the extracellular domain of the polypeptide is fused with another compound, such as a compound to

increase the half-life of the polypeptide (for example, polyethylene glycol), or (iv) polypeptides in which the additional amino acids are fused to the extracellular domain of the polypeptide, such as an IgG Fc fusion region peptide or leader or secretory sequence or a sequence which is employed for purification of the extracellular domain of the polypeptide or a proprotein sequence.

[0160] Antibodies of the present invention may bind fragments, derivatives or analogs of the polypeptide of SEQ ID NO:3229, or that encoded by the deposited cDNA plasmid, such as (i) polypeptides in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code, or (ii) polypeptides in which one or more of the amino acid residues includes a substituent group, or (iii) polypeptides in which the extracellular domain of the polypeptide is fused with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol), or (iv) polypeptides in whieh the additional amino acids are fused to the extracellular domain of the polypeptide, such as, a soluble biologically active fragment of another TNF ligand family member (e.g., CD40 Ligand), an IgG Fc fusion region peptide or leader or secretory sequence or a sequence which is employed for purifieation of the extracellular domain of the polypeptide or a proprotein sequence. Such fragments, derivatives and analogs are deemed to be within the scope of those skilled in the art from the teachings herein.

[0161] Thus, the antibodies of the invention may bind BLyS polypeptides that include one or more amino acid substitutions, deletions or additions, either from natural mutations or human manipulation. As indicated, changes are preferably of a minor nature, such as conservative amino acid substitutions that do not significantly affect the folding or activity of the protein (see Table 13).

TABLE 13. Conservative Amino Acid Substitutions.

Aromatic	Phenylalanine Tryptophan Tyrosine
Hydrophobic	Leucine Isoleucine Valine
Polar	Glutamine Asparagine
Basic	Arginine Lysine Histidine
Acidic	Aspartic Acid Glutamie Acid
Small	Alanine Serine Threonine Methionine Glycine

[0162] In one embodiment of the invention, antibodies of the present invention bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of a BLyS polypeptide having an amino acid sequence which contains at least one conservative amino acid substitution, but not more than 50 conservative amino acid substitutions, even more preferably, not more than 40 conservative amino acid substitutions, still more preferably, not more than 30 conservative amino acid substitutions, and still even more preferably, not more than 20 conservative amino acid substitutions. In one embodiment of the invention, antibodies of the present invention bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of a BLyS polypeptide having an amino acid sequence which contains at least one conservative amino acid substitution, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 conservative amino acid substitutions.

[0163] For example, site directed changes at the amino acid level of BLyS can be made by replacing a particular amino acid with a conservative substitution. Antibodies of the present invention may bind BLyS amino acid sequences containing conservative substitution mutations of the polypeptide of SEQ ID NO:3228 including: M1 replaced

with A, G, I, L, S, T, or V; D2 replaced with E; D3 replaced with E; S4 replaced with A, G, I, L, T, M, or V; T5 replaced with A, G, I, L, S, M, or V; E6 replaced with D; R7 replaced with H, or K; E8 replaced with D; Q9 replaced with N; S10 replaced with A, G, I, L, T, M, or V; R11 replaced with H, or K; L12 replaced with A, G, I, S, T, M, or V; T13 replaced with A, G, I, L, S, M, or V; S14 replaced with A, G, I, L, T, M, or V; L16 replaced with A, G, I, S, T, M, or V; K17 replaeed with H, or R; K18 replaced with H, or R; R19 replaced with H, or K; E20 replaced with D; E21 replaced with D; M22 replaced with A, G, I, L, S, T, or V; K23 replaced with H, or R; L24 replaced with A, G, I, S, T, M, or V; K25 replaced with H, or R; E26 replaced with D; V28 replaced with A, G, I, L, S, T, or M; S29 replaced with A, G, I, L, T, M, or V; I30 replaced with A, G, L, S, T, M, or V; L31 replaced with A, G, I, S, T, M, or V; R33 replaced with H, or K; K34 replaced with H, or R; E35 replaced with D; S36 replaced with A, G, I, L, T, M, or V; S38 replaced with A, G, I, L, T, M, or V; V39 replaced with A, G, I, L, S, T, or M; R40 replaced with H, or K; S41 replaced with A, G, I, L, T, M, or V; S42 replaced with A, G, I, L, T, M, or V; K43 replaced with H, or R; D44 replaced with E; G45 replaced with A, I, L, S, T, M, or V; K46 replaced with H, or R; L47 replaced with A, G, I, S, T, M, or V; L48 replaced with A, G, I, S, T, M, or V; A49 replaced with G, I, L, S, T, M, or V; A50 replaced with G, I, L, S, T, M, or V; T51 replaced with A, G, I, L, S, M, or V; L52 replaced with A, G, I, S, T, M, or V; L53 replaced with A, G, I, S, T, M, or V; L54 replaced with A, G, I, S, T, M, or V; A55 replaced with G, I, L, S, T, M, or V; L56 replaced with A, G, I, S, T, M, or V; L57 replaced with A, G, I, S, T, M, or V; S58 replaced with A, G, I, L, T, M, or V; L61 replaced with A, G, I, S, T, M, or V; T62 replaced with A, G, I, L, S, M, or V; V63 replaced with A, G, I, L, S, T, or M; V64 replaced with A, G, I, L, S, T, or M; S65 replaced with A, G, I, L, T, M, or V; F66 replaced with W, or Y; Y67 replaced with F, or W; Q68 replaced with N; V69 replaced with A, G, I, L, S, T, or M; A70 replaced with G, I, L, S, T, M, or V; A71 replaced with G, I, L, S, T, M, or V; L72 replaced with A, G, I, S, T, M, or V; Q73 replaced with N; G74 replaced with A, I, L, S, T, M, or V; D75 replaced with E; L76 replaced with A, G, I, S, T, M, or V; A77 replaced with G, I, L, S, T, M, or V; S78 replaced with A, G, I, L, T, M, or V; L79 replaced with A, G, I, S, T, M, or V; R80 replaced with H, or K; A81 replaced with G, I, L, S, T, M, or V; E82 replaced with D; L83 replaced with A, G, I, S, T, M, or V; Q84 replaced with N; G85 replaced with A, I, L, S, T, M, or V; H86 replaced with K, or R; H87 replaced with K, or R; A88 replaced with G,

I, L, S, T, M, or V; E89 replaced with D; K90 replaced with H, or R; L91 replaced with A, G, I, S, T, M, or V; A93 replaced with G, I, L, S, T, M, or V; G94 replaced with A, I, L, S, T, M, or V; A95 replaced with G, I, L, S, T, M, or V; G96 replaced with A, I, L, S, T, M, or V; A97 replaeed with G, I, L, S, T, M, or V; K99 replaced with H, or R; A100 replaced with G, I, L, S, T, M, or V; G101 replaced with A, I, L, S, T, M, or V; L102 replaced with A, G, I, S, T, M, or V; E103 replaced with D; E104 replaced with D; A105 replaced with G, I, L, S, T, M, or V; A107 replaced with G, I, L, S, T, M, or V; V108 replaced with A, G, I, L, S, T, or M; T109 replaced with A, G, I, L, S, M, or V; A110 replaced with G, I, L, S, T, M, or V; G111 replaced with A, I, L, S, T, M, or V; L112 replaced with A, G, I, S, T, M, or V; K113 replaced with H, or R; I114 replaced with A, G, L, S, T, M, or V; F115 replaced with W, or Y; E116 replaced with D; A119 replaeed with G, I, L, S, T, M, or V; G121 replaced with A, I, L, S, T, M, or V; E122 replaced with D; G123 replaced with A, I, L, S, T, M, or V; N124 replaced with Q; S125 replaced with A, G, I, L, T, M, or V; S126 replaced with A, G, I, L, T, M, or V; Q127 replaced with N; N128 replaced with Q; S129 replaced with A, G, I, L, T, M, or V; R130 replaced with H, or K; N131 replaced with Q; K132 replaced with H, or R; R133 replaced with H, or K; A134 replaced with G, I, L, S, T, M, or V; V135 replaced with A, G, I, L, S, T, or M; Q136 replaced with N; G137 replaced with A, I, L, S, T, M, or V; E139 replaced with D; E140 replaced with D; T141 replaced with A, G, I, L, S, M, or V; V142 replaced with A, G, I, L, S, T, or M; T143 replaced with A, G, I, L, S, M, or V; Q144 replaced with N; D145 replaced with E; L147 replaeed with A, G, I, S, T, M, or V; Q148 replaced with N; L149 replaced with A, G, I, S, T, M, or V; I150 replaced with A, G, L, S, T, M, or V; A151 replaced with G, I, L, S, T, M, or V; D152 replaced with E; S153 replaced with A, G, I, L, T, M, or V; E154 replaced with D; T155 replaced with A, G, I, L, S, M, or V; T157 replaced with A, G, I, L, S, M, or V; I158 replaced with A, G, L, S, T, M, or V; Q159 replaced with N; K160 replaced with H, or R; G161 replaced with A, I, L, S, T, M, or V; S162 replaced with A, G, I, L, T, M, or V; Y163 replaced with F, or W; T164 replaced with A, G, I, L, S, M, or V; F165 replaced with W, or Y; V166 replaced with A, G, I, L, S, T, or M; W168 replaced with F, or Y; L169 replaced with A, G, I, S, T, M, or V; L170 replaced with A, G, I, S, T, M, or V; S171 replaeed with A, G, I, L, T, M, or V; F172 replaced with W, or Y; K173 replaced with H, or R; R174 replaced with H, or K; G175 replaced with A, I, L, S, T, M, or V; S176 replaced with A, G, I, L, T, M, or V; A177 replaced with G, I, L, S, T, M, or

V; L178 replaced with A, G, I, S, T, M, or V; E179 replaced with D; E180 replaced with D; K181 replaced with H, or R; E182 replaced with D; N183 replaced with Q; K184 replaced with H, or R; I185 replaced with A, G, L, S, T, M, or V; L186 replaced with A, G, I, S, T, M, or V; V187 replaced with A, G, I, L, S, T, or M; K188 replaced with H, or R; E189 replaced with D; T190 replaced with A, G, I, L, S, M, or V; G191 replaced with A, I, L, S, T, M, or V; Y192 replaced with F, or W; F193 replaced with W, or Y; F194 replaced with W, or Y; I195 replaeed with A, G, L, S, T, M, or V; Y196 replaced with F, or W; G197 replaced with A, I, L, S, T, M, or V; Q198 replaced with N; V199 replaced with A, G, I, L, S, T, or M; L200 replaced with A, G, I, S, T, M, or V; Y201 replaced with F, or W; T202 replaced with A, G, I, L, S, M, or V; D203 replaeed with E; K204 replaced with H, or R; T205 replaced with A, G, I, L, S, M, or V; Y206 replaced with F, or W; A207 replaced with G, I, L, S, T, M, or V; M208 replaced with A, G, I, L, S, T, or V; G209 replaced with A, I, L, S, T, M, or V; H210 replaced with K, or R; L211 replaced with A, G, I, S, T, M, or V; I212 replaced with A, G, L, S, T, M, or V; Q213 replaced with N; R214 replaced with H, or K; K215 replaced with H, or R; K216 replaced with H, or R; V217 replaced with A, G, I, L, S, T, or M; H218 replaced with K, or R; V219 replaeed with A, G, I, L, S, T, or M; F220 replaced with W, or Y; G221 replaeed with A, I, L, S, T, M, or V; D222 replaced with E; E223 replaced with D; L224 replaced with A, G, I, S, T, M, or V; S225 replaced with A, G, I, L, T, M, or V; L226 replaeed with A, G, I, S, T, M, or V; V227 replaced with A, G, I, L, S, T, or M; T228 replaced with A, G, I, L, S, M, or V; L229 replaced with A, G, I, S, T, M, or V; F230 replaced with W, or Y; R231 replaeed with H, or K; I233 replaced with A, G, L, S, T, M, or V; Q234 replaced with N; N235 replaced with Q; M236 replaced with A, G, I, L, S, T, or V; E238 replaced with D; T239 replaced with A, G, I, L, S, M, or V; L240 replaced with A, G, I, S, T, M, or V; N242 replaced with Q; N243 replaced with Q; S244 replaced with A, G, I, L, T, M, or V; Y246 replaced with F, or W; S247 replaced with A, G, I, L, T, M, or V; A248 replaced with G, I, L, S, T, M, or V; G249 replaced with A, I, L, S, T, M, or V; I250 replaced with A, G, L, S, T, M, or V; A251 replaced with G, I, L, S, T, M, or V; K252 replaced with H, or R; L253 replaced with A, G, I, S, T, M, or V; E254 replaced with D; E255 replaced with D; G256 replaeed with A, I, L, S, T, M, or V; D257 replaced with E; E258 replaced with D; L259 replaced with A, G, I, S, T, M, or V; Q260 replaced with N; L261 replaced with A, G, I, S, T, M, or V; A262 replaeed with G, I, L, S, T, M, or V; I263 replaced with A, G, L,

S, T, M, or V; R265 replaced with H, or K; E266 replaeed with D; N267 replaced with Q; A268 replaced with G, I, L, S, T, M, or V; Q269 replaced with N; I270 replaced with A, G, L, S, T, M, or V; S271 replaced with A, G, I, L, T, M, or V; L272 replaced with A, G, I, S, T, M, or V; D273 replaced with E; G274 replaced with A, I, L, S, T, M, or V; D275 replaced with E; V276 replaced with A, G, I, L, S, T, or M; T277 replaced with A, G, I, L, S, M, or V; F278 replaced with W, or Y; F279 replaced with W, or Y; G280 replaced with A, I, L, S, T, M, or V; A281 replaced with G, I, L, S, T, M, or V; L282 replaced with A, G, I, S, T, M, or V; K283 replaced with H, or R; L284 replaced with A, G, I, S, T, M, or V; and/or L285 replaced with A, G, I, S, T, M, or V.

[0164] In another embodiment, site directed ehanges at the amino acid level of BLyS can be made by replacing a particular amino aeid with a conservative substitution. Antibodies of the present invention may bind BLyS amino acid sequences containing conservative substitution mutations of the polypeptide of SEQ ID NO:3229 including: M1 replaced with A, G, I, L, S, T, or V; D2 replaced with E; D3 replaced with E; S4 replaced with A, G, I, L, T, M, or V; T5 replaced with A, G, I, L, S, M, or V; E6 replaced with D; R7 replaced with H, or K; E8 replaced with D; Q9 replaced with N; S10 replaced with A, G, I, L, T, M, or V; R11 replaced with H, or K; L12 replaced with A, G, I, S, T, M, or V; T13 replaced with A, G, I, L, S, M, or V; S14 replaced with A, G, I, L, T, M, or V; L16 replaced with A, G, I, S, T, M, or V; K17 replaced with H, or R; K18 replaced with H, or R; R19 replaced with H, or K; E20 replaced with D; E21 replaced with D; M22 replaced with A, G, I, L, S, T, or V; K23 replaced with H, or R; L24 replaced with A, G, I, S, T, M, or V; K25 replaced with H, or R; E26 replaced with D; V28 replaced with A, G, I, L, S, T, or M; S29 replaced with A, G, I, L, T, M, or V; I30 replaced with A, G, L, S, T, M, or V; L31 replaced with A, G, I, S, T, M, or V; R33 replaced with H, or K; K34 replaced with H, or R; E35 replaced with D; S36 replaced with A, G, I, L, T, M, or V; S38 replaced with A, G, I, L, T, M, or V; V39 replaced with A, G, I, L, S, T, or M; R40 replaced with H, or K; S41 replaced with A, G, I, L, T, M, or V; S42 replaced with A, G, I, L, T, M, or V; K43 replaced with H, or R; D44 replaced with E; G45 replaced with A, I, L, S, T, M, or V; K46 replaced with H, or R; L47 replaced with A, G, I, S, T, M, or V; L48 replaced with A, G, I, S, T, M, or V; A49 replaced with G, I, L, S, T, M, or V; A50 replaced with G, I, L, S, T, M, or V; T51 replaced with A, G, I, L, S, M, or V; L52 replaced with A, G, I, S, T, M, or V; L53 replaced with A, G, I, S, T, M, or V; L54 replaced with A, G, I, S, T, M, or V; A55

replaced with G, I, L, S, T, M, or V; L56 replaced with A, G, I, S, T, M, or V; L57 replaced with A, G, I, S, T, M, or V; S58 replaced with A, G, I, L, T, M, or V; L61 replaced with A, G, I, S, T, M, or V; T62 replaced with A, G, I, L, S, M, or V; V63 replaced with A, G, I, L, S, T, or M; V64 replaced with A, G, I, L, S, T, or M; S65 replaced with A, G, I, L, T, M, or V; F66 replaced with W, or Y; Y67 replaced with F, or W; Q68 replaced with N; V69 replaced with A, G, I, L, S, T, or M; A70 replaced with G, I, L, S, T, M, or V; A71 replaced with G, I, L, S, T, M, or V; L72 replaced with A, G, I, S, T, M, or V; Q73 replaced with N; G74 replaced with A, I, L, S, T, M, or V; D75 replaced with E; L76 replaced with A, G, I, S, T, M, or V; A77 replaced with G, I, L, S, T, M, or V; S78 replaced with A, G, I, L, T, M, or V; L79 replaeed with A, G, I, S, T, M, or V; R80 replaced with H, or K; A81 replaced with G, I, L, S, T, M, or V; E82 replaced with D; L83 replaced with A, G, I, S, T, M, or V; Q84 replaced with N; G85 replaced with A, I, L, S, T, M, or V; H86 replaced with K, or R; H87 replaced with K, or R; A88 replaced with G, I, L, S, T, M, or V; E89 replaced with D; K90 replaced with H, or R; L91 replaced with A, G, I, S, T, M, or V; A93 replaced with G, I, L, S, T, M, or V; G94 replaced with A, I, L, S, T, M, or V; A95 replaced with G, I, L, S, T, M, or V; G96 replaced with A, I, L, S, T, M, or V; A97 replaced with G, I, L, S, T, M, or V; K99 replaced with H, or R; A100 replaced with G, I, L, S, T, M, or V; G101 replaced with A, I, L, S, T, M, or V; L102 replaced with A, G, I, S, T, M, or V; E103 replaced with D; E104 replaced with D; A105 replaced with G, I, L, S, T, M, or V; A107 replaced with G, I, L, S, T, M, or V; V108 replaced with A, G, I, L, S, T, or M; T109 replaced with A, G, I, L, S, M, or V; A110 replaced with G, I, L, S, T, M, or V; G111 replaced with A, I, L, S, T, M, or V; L112 replaced with A, G, I, S, T, M, or V; K113 replaced with H, or R; I114 replaced with A, G, L, S, T, M, or V; F115 replaced with W, or Y; E116 replaced with D; A119 replaced with G, I, L, S, T, M, or V; G121 replaced with A, I, L, S, T, M, or V; E122 replaced with D; G123 replaced with A, I, L, S, T, M, or V; N124 replaced with Q; S125 replaced with A, G, I, L, T, M, or V; S126 replaced with A, G, I, L, T, M, or V; Q127 replaced with N; N128 replaced with Q; S129 replaced with A, G, I, L, T, M, or V; R130 replaced with H, or K; N131 replaced with Q; K132 replaced with H, or R; R133 replaced with H, or K; A134 replaced with G, I, L, S, T, M, or V; V135 replaced with A, G, I, L, S, T, or M; Q136 replaced with N; G137 replaced with A, I, L, S, T, M, or V; E139 replaced with D; E140 replaced with D; T141 replaced with A, G, I, L, S, M, or V; G142 replaced with A, I, L, S, T, M, or V;

S143 replaced with A, G, I, L, T, M, or V; Y144 replaced with F, or W; T145 replaced with A, G, I, L, S, M, or V; F146 replaced with W, or Y; V147 replaced with A, G, I, L, S, T, or M; W149 replaced with F, or Y; L150 replaced with A, G, I, S, T, M, or V; L151 replaced with A, G, I, S, T, M, or V; S152 replaced with A, G, I, L, T, M, or V; F153 replaced with W, or Y; K154 replaced with H, or R; R155 replaced with H, or K; G156 replaced with A, I, L, S, T, M, or V; S157 replaced with A, G, I, L, T, M, or V; A158 replaced with G, I, L, S, T, M, or V; L159 replaced with A, G, I, S, T, M, or V; E160 replaced with D; E161 replaced with D; K162 replaced with H, or R; E163 replaced with D; N164 replaced with Q; K165 replaced with H, or R; I166 replaced with A, G, L, S, T, M, or V; L167 replaced with A, G, I, S, T, M, or V; V168 replaced with A, G, I, L, S, T, or M; K169 replaced with H, or R; E170 replaced with D; T171 replaced with A, G, I, L, S, M, or V; G172 replaced with A, I, L, S, T, M, or V; Y173 replaced with F, or W; F174 replaced with W, or Y; F175 replaced with W, or Y; I176 replaced with A, G, L, S, T, M, or V; Y177 replaced with F, or W; G178 replaced with A, I, L, S, T, M, or V; Q179 replaced with N; V180 replaced with A, G, I, L, S, T, or M; L181 replaced with A, G, I, S, T, M, or V; Y182 replaced with F, or W; T183 replaced with A, G, I, L, S, M, or V; D184 replaced with E; K185 replaced with H, or R; T186 replaced with A, G, I, L, S, M, or V; Y187 replaced with F, or W; A188 replaced with G, I, L, S, T, M, or V; M189 replaced with A, G, I, L, S, T, or V; G190 replaced with A, I, L, S, T, M, or V; H191 replaced with K, or R; L192 replaced with A, G, I, S, T, M, or V; I193 replaced with A, G, L, S, T, M, or V; Q194 replaced with N; R195 replaced with H, or K; K196 replaced with H, or R; K197 replaced with H, or R; V198 replaced with A, G, I, L, S, T, or M; H199 replaced with K, or R; V200 replaced with A, G, I, L, S, T, or M; F201 replaced with W, or Y; G202 replaced with A, I, L, S, T, M, or V; D203 replaced with E; E204 replaced with D; L205 replaced with A, G, I, S, T, M, or V; S206 replaced with A, G, I, L, T, M, or V; L207 replaced with A, G, I, S, T, M, or V; V208 replaced with A, G, I, L, S, T, or M; T209 replaced with A, G, I, L, S, M, or V; L210 replaced with A, G, I, S, T, M, or V; F211 replaced with W, or Y; R212 replaced with H, or K; I214 replaced with A, G, L, S, T, M, or V; Q215 replaced with N; N216 replaced with Q; M217 replaced with A, G, I, L, S, T, or V; E219 replaced with D; T220 replaced with A, G, I, L, S, M, or V; L221 replaced with A, G, I, S, T, M, or V; N223 replaced with Q; N224 replaced with Q; S225 replaced with A, G, I, L, T, M, or V; Y227 replaced with F, or W; S228 replaced with A, G, I, L, T,

M, or V; A229 replaced with G, I, L, S, T, M, or V; G230 replaced with A, I, L, S, T, M, or V; I231 replaced with A, G, L, S, T, M, or V; A232 replaced with G, I, L, S, T, M, or V; K233 replaeed with H, or R; L234 replaced with A, G, I, S, T, M, or V; E235 replaced with D; E236 replaced with D; G237 replaced with A, I, L, S, T, M, or V; D238 replaced with E; E239 replaced with D; L240 replaced with A, G, I, S, T, M, or V; Q241 replaced with N; L242 replaeed with A, G, I, S, T, M, or V; A243 replaced with G, I, L, S, T, M, or V; I244 replaced with A, G, L, S, T, M, or V; R246 replaced with H, or K; E247 replaced with D; N248 replaced with Q; A249 replaced with G, I, L, S, T, M, or V; Q250 replaced with N; I251 replaced with A, G, L, S, T, M, or V; S252 replaced with A, G, I, L, T, M, or V; L253 replaced with A, G, I, S, T, M, or V; D254 replaced with E; G255 replaced with A, I, L, S, T, M, or V; D256 replaced with E; V257 replaced with A, G, I, L, S, T, or M; T258 replaced with A, G, I, L, S, M, or V; F259 replaced with W, or Y; F260 replaced with W, or Y; G261 replaced with A, I, L, S, T, M, or V; A262 replaced with G, I, L, S, T, M, or V; L263 replaced with A, G, I, S, T, M, or V; K264 replaced with H, or R; L265 replaced with A, G, I, S, T, M, or V; and/or L266 replaced with A, G, I, S, T, M, or V.

[0165] In another embodiment, site directed changes at the amino acid level of BLyS can be made by replacing a particular amino acid with a conservative substitution. Antibodies of the present invention may bind BLyS amino acid sequences eontaining conservative substitution mutations of the polypeptide of any one of SEQ ID NOS:3230-3237.

[0166] Amino acids in the BLyS polypeptides that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham and Wells, *Science 244*:1081-1085 (1989)). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for functional activity, such ligand binding and the ability to stimulate lymphocyte (e.g., B cell) as, for example, proliferation, differentiation, and/or activation. Accordingly, antibodies of the present invention may bind amino acids in the BLyS polypeptides that are essential for function. In preferred embodiments, antibodies of the present invention bind amino acids in the BLyS polypeptides that are essential for function and inhibit BLyS polypeptide function. In other preferred embodiments, antibodies of the present invention bind amino acids in the BLyS polypeptides that are essential for funetion and enhance BLyS polypeptide function.

[0167] Of special interest are substitutions of charged amino acids with other charged or neutral amino acids which may produce proteins with highly desirable improved characteristics, such as less aggregation. Aggregation may not only reduce activity but also be problematic when preparing pharmaceutieal formulations, because aggregates can be immunogenie (Pinekard *et al., Clin. Exp. Immunol. 2*:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland *et al., Crit. Rev. Therapeutic Drug Carrier Systems 10*:307-377 (1993).

[0168] In another embodiment, the invention provides for antibodies that bind polypeptides having amino acid sequences containing non-conservative substitutions of the amino acid sequence provided in SEQ ID NO:3228. For example, non-conservative substitutions of the BLyS protein sequence provided in SEQ ID NO:3228 include: M1 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D2 replaeed with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D3 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S4 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T5 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E6 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R7 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E8 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Q9 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S10 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R11 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L12 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T13 replaeed with D, E, H, K, R, N, Q, F, W, Y, P, or C; S14 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C15 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; L16 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K17 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K18 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R19 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E20 replaeed with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E21 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; M22 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K23 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L24 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K25 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E26 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C27 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; V28 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S29 replaced with D, E, H,

K, R, N, Q, F, W, Y, P, or C; I30 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L31 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P32 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; R33 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K34 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E35 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S36 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P37 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; S38 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V39 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R40 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S41 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S42 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K43 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D44 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G45 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K46 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L47 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L48 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A49 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A50 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T51 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L52 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L53 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L54 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A55 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L56 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L57 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S58 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C59 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; C60 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; L61 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T62 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V63 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V64 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S65 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F66 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; Y67 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; Q68 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; V69 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A70 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A71 replaeed with D, E, H, K, R, N, Q, F, W, Y, P, or C; L72 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q73 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G74 replaced with D, E, H, K, R, N, Q, F, W, Y, P,

or C; D75 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L76 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A77 replaeed with D, E, H, K, R, N, Q, F, W, Y, P, or C; S78 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L79 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R80 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A81 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E82 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L83 replaeed with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q84 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G85 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H86 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; H87 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A88 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E89 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K90 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L91 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P92 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; A93 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G94 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A95 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G96 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A97 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P98 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; K99 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A100 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G101 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L102 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E103 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E104 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A105 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P106 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; A107 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V108 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T109 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A110 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G111 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L112 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K113 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I114 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F115 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; E116 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P117 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; P118 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q,

F, W, Y, or C; A119 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P120 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; G121 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E122 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G123 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N124 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S125 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S126 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q127 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; N128 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S129 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R130 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N131 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; K132 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R133 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A134 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V135 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q136 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G137 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P138 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; E139 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E140 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T141 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V142 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T143 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q144 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; D145 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C146 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; L147 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q148 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L149 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I150 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A151 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D152 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S153 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E154 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T155 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P156 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; T157 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I158 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q159 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; K160 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G161

replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S162 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y163 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; T164 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F165 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; V166 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P167 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; W168 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; L169 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L170 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S171 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F172 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; K173 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R174 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G175 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S176 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A177 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L178 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E179 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E180 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K181 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E182 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N183 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; K184 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I185 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L186 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V187 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K188 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E189 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T190 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G191 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y192 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; F193 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; F194 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; I195 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y196 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; G197 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q198 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; V199 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L200 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y201 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; T202 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D203 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K204 replaced with D, E, A, G, I, L,

S, T, M, V, N, Q, F, W, Y, P, or C; T205 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y206 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; A207 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; M208 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G209 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H210 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L211 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I212 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q213 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; R214 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K215 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K216 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V217 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H218 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V219 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F220 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; G221 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D222 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E223 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L224 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S225 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L226 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V227 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T228 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L229 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F230 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; R231 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C232 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; I233 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q234 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; N235 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; M236 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P237 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; E238 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T239 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L240 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P241 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; N242 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; N243 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S244 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C245 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; Y246 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; S247

replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A248 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G249 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I250 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A251 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K252 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L253 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E254 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E255 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G256 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D257 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E258 replaeed with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L259 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q260 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L261 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A262 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I263 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P264 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; R265 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E266 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N267 replaeed with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; A268 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q269 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; I270 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S271 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L272 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D273 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G274 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D275 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V276 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T277 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F278 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; F279 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; G280 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A281 replaeed with D, E, H, K, R, N, Q, F, W, Y, P, or C; L282 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K283 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L284 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; and/or L285 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C.

[0169] In an additional embodiment, antibodies of the present invention bind BLyS polypeptides comprising, or alternatively consisting of, a BLyS amino acid sequence in which more than one amino acid (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30 and 50) is

replaced with the substituted amino acids as described above (either conservative or nonconservative).

[0170] In another embodiment of the invention, antibodies of the present invention bind BLyS polypeptides with non-conservative substitutions of the sequence provided in SEQ ID NO:3229 including: M1 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D2 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D3 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S4 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T5 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E6 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R7 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E8 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Q9 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S10 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R11 replaeed with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L12 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T13 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S14 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C15 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; L16 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K17 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K18 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R19 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E20 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E21 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; M22 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K23 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L24 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K25 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E26 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C27 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; V28 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S29 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I30 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L31 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P32 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; R33 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K34 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E35 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S36 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P37 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; S38 replaced

with D, E, H, K, R, N, Q, F, W, Y, P, or C; V39 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R40 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S41 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S42 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K43 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D44 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G45 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K46 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L47 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L48 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A49 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A50 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T51 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L52 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L53 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L54 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A55 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L56 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L57 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S58 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C59 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; C60 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; L61 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T62 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V63 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V64 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S65 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F66 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; Y67 replaeed with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; Q68 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; V69 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A70 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A71 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L72 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q73 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G74 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D75 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L76 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A77 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S78 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L79 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R80 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A81 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E82 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L83 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q84

replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G85 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H86 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; H87 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A88 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E89 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K90 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L91 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P92 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; A93 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G94 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A95 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G96 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A97 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P98 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; K99 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A100 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G101 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L102 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E103 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E104 replaeed with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A105 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P106 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; A107 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V108 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T109 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A110 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G111 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L112 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K113 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I114 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F115 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; E116 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P117 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; P118 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; A119 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P120 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; G121 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E122 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G123 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N124 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S125 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S126 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q127 replaced with D, E,

H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; N128 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S129 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R130 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N131 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; K132 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R133 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A134 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V135 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q136 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G137 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P138 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; E139 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E140 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T141 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G142 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S143 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y144 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; T145 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F146 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; V147 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P148 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; W149 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; L150 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L151 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S152 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F153 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; K154 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R155 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G156 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S157 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A158 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L159 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E160 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E161 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K162 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E163 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N164 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; K165 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I166 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L167 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V168 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K169 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or

C; E170 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T171 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G172 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y173 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; F174 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; F175 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; I176 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y177 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; G178 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q179 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; V180 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L181 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y182 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; T183 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D184 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K185 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T186 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y187 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; A188 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; M189 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G190 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H191 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L192 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I193 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q194 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; R195 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K196 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K197 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V198 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H199 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V200 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F201 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; G202 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D203 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E204 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L205 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S206 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L207 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V208 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T209 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L210 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F211 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; R212 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C213 replaced with D, E, H, K, R, A, G,

I, L, S, T, M, V, N, Q, F, W, Y, or P; I214 replaeed with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q215 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; N216 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; M217 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P218 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; E219 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T220 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L221 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P222 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; N223 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; N224 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S225 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C226 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; Y227 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; S228 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A229 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G230 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I231 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A232 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K233 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L234 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E235 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E236 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G237 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D238 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E239 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L240 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q241 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L242 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A243 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I244 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P245 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; R246 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E247 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N248 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; A249 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q250 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; I251 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S252 replaeed with D, E, H, K, R, N, Q, F, W, Y, P, or C; L253 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D254 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G255 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D256

replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V257 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T258 replaeed with D, E, H, K, R, N, Q, F, W, Y, P, or C; F259 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; F260 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; G261 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A262 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L263 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K264 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L265 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; and/or L266 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C.

[0171] In another embodiment, site directed changes at the amino acid level of BLyS can be made by replacing a particular amino acid with a non-conservative substitution. Antibodies of the present invention may bind BLyS amino acid sequences containing non-conservative substitution mutations of the polypeptide of any one of SEQ ID NOS:3230-3237.

[0172] In an additional embodiment, antibodies of the present invention bind BLyS polypeptides comprising, or alternatively consisting of, a BLyS amino acid sequence in which more than one amino acid (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30 and 50) is replaced with the substituted amino acids as described above (either conservative or nonconservative).

[0173] Replacement of amino acids can also change the selectivity of the binding of a ligand to cell surface receptors. For example, Ostade *et al., Nature 361*:266-268 (1993) describes certain mutations resulting in selective binding of TNF-alpha to only one of the two known types of TNF receptors. Since BLyS is a member of the TNF polypeptide family, mutations similar to those in TNF-alpha are likely to have similar effects in BLyS polypeptides.

[0174] Sites that are critical for ligand-receptor binding can also be determined by structural analysis such as crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith *et al., J. Mol. Biol. 224*:899-904 (1992) and de Vos *et al. Science 255*:306-312 (1992)).

[0175] Since BLyS is a member of the TNF-related protein family, mutations may be made in sequences encoding amino acids in the TNF conserved domain, e.g., in positions Gly-191 through Leu-284 of SEQ ID NO:3228 or in positions Gly-172 through Leu-265 of SEQ ID NO:3229, may modulate rather than completely eliminate functional activities

(e.g., biological activities) of BLyS polypeptides or fragments or variants thereof. Accordingly, antibodies of the present invention may bind BLyS polypeptides that have mutations in the TNF conserved domain. In preferred embodiments, antibodies of the present invention may bind BLyS polypeptides that have mutations in the TNF conserved domain and act as antagonists of BLyS. In other preferred embodiments, antibodies of the present invention may bind BLyS polypeptides that have mutations in the TNF conserved domain and act as agonists of BLyS.

[0176] Recombinant DNA technology known to those skilled in the art (see, for instance, DNA shuffling *supra*) can be used to create novel mutant proteins or muteins including single or multiple amino acid substitutions, deletions, additions or fusion proteins. Such modified polypeptides can show, e.g., enhanced activity or increased stability. In addition, they may be purified in higher yields and show better solubility than the corresponding natural polypeptide, at least under certain purification and storage conditions.

[0177] Thus, the invention also encompasses antibodies that bind BLyS derivatives and analogs that have one or more amino acid residues deleted, added, or substituted to generate BLyS polypeptides, e.g., that are better suited for expression, scale up, etc., in the host cells. For example, cysteine residues can be deleted or substituted with another amino acid residue in order to eliminate disulfide bridges; N-linked glycosylation sites can be altered or eliminated to achieve, for example, expression of a homogeneous product that is more easily recovered and purified from yeast hosts which are known to hyperglycosylate N-linked sites. To this end, a variety of amino acid substitutions at one or both of the first or third amino acid positions on any one or more of the glycosylation recognition sequences in the BLyS polypeptides of the invention, and/or an amino acid deletion at the second position of any one or more such recognition sequences will prevent glycosylation of the BLyS at the modified tripeptide sequence (see, e.g., Miyajimo et al., EMBO J 5(6):1193-1197). By way of non-limiting example, mutation of the serine at position 244 to alanine either singly or in combination with mutation of the asparagine at position 242 to glutamine abolishes glycosylation of the mature soluble form of BLyS (e.g., amino acids 134-285 of SEQ ID NO:3228) when expressed in the yeast *Pichea pastoris*. A mutant BLyS polypeptide in which only the asparagine at position 242 is mutated to glutamine, is still gycosylated when expressed in *Pichea pastoris*. In this

mutant, the glycosylation event may be due to the activation or unmasking of an O-linked glyscosylation site at serine 244. Similar mutations affecting glycosylation could also be made in the BLyS polypeptide of SEQ ID NO:3229, i.e., aspargine-223 to glutamine and/or serine-224 to alanine of SEQ ID NO:3229. Additionally, one or more of the amino acid residues of the polypeptides of the invention (e.g., arginine and lysine residues) may be deleted or substituted with another residue to eliminate undesired processing by proteases such as, for example, furins or kexins. One possible result of such a mutation is that BLyS polypeptide of the invention is not cleaved and released from the cell surface. Accordingly, antibodies of the invention may bind BLyS derivatives and analogs that have one or more amino acid residues deleted, added, or substituted. In other embodiments, antibodies of the invention may bind BLyS derivatives, variants or analogs that are unable to be cleaved from the cell surface.

[0178] In a specific embodiment, antibodies of the invention bind BLyS polypeptides in which Lys-132 and/or Arg-133 of the BLyS sequence shown in SEQ ID NO:3228 is mutated to another amino acid residue, or deleted altogether, to prevent or diminish release of the soluble form of BLyS from cells expressing BLyS. In a more specific embodiment, antibodies of the invention bind BLyS polypeptides in which Lys-132 of the BLyS sequence shown in SEQ ID NO:3228 is mutated to Ala-132. In another, nonexclusive specific embodiment, antibodies of the invention bind BLyS polypeptides in which Arg-133 of the BLyS sequence shown in SEQ ID NO:3228 is mutated to Ala-133. These mutated proteins have uses such as, for example, in ex vivo therapy or gene therapy, to engineer cells expressing a BLyS polypeptide that is retained on the surface of the engineered cells.

[0179] In a specific embodiment, antibodies of the invention bind BLyS polypeptides in which Cys-146 of the BLyS sequence shown in SEQ ID NO:3228 is mutated to another amino acid residue, or deleted altogether, for example, to aid preventing or diminishing oligomerization of the mutant BLyS polypeptide when expressed in an expression system. In a specific embodiment, antibodies of the invention bind BLyS polypeptides in which Cys-146 is replaced with a serine amino acid residue.

[0180] In another specific embodiment, antibodies of the invention bind BLyS polypeptides in which Cys-232 of the BLyS sequence shown in SEQ ID NO:3228 is mutated to another amino acid residue, or deleted altogether, for example, to aid

preventing or diminishing oligomerization of the mutant BLyS polypeptide when expressed in an expression system. In a specific embodiment, antibodies of the invention bind BLyS polypeptides in which Cys-232 is replaced with a serine amino acid residue. Polypeptides encoding these polypeptides are also encompassed by the invention.

[0181] In yet another specific embodiment, antibodies of the invention bind BLyS polypeptides in which Cys-245 of the BLyS sequence shown in SEQ ID NO:3228 is mutated to another amino acid residue, or deleted altogether, for example, to aid preventing or diminishing oligomerization of the mutant BLyS polypeptide when expressed in an expression system. In a specific embodiment, antibodies of the invention bind BLyS polypeptides in which Cys-245 is replaced with a serine amino acid residue. Polypeptides encoding these polypeptides are also encompassed by the invention.

[0182] The polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of the BLyS polypeptides can be substantially purified by the one-step method described in Smith and Johnson, *Gene 67*:31-40 (1988).

[0183] The antibodies of the present invention bind BLyS polypeptides including the complete polypeptide encoded by the deposited cDNA (ATCC Deposit No. 97768) including the intracellular, transmembrane and extracellular domains of the polypeptide encoded by the deposited cDNA, the mature soluble polypeptide encoded by the deposited cDNA, the extracellular domain minus the intracellular and transmembrane domains of the protein, the complete polypeptide of SEQ ID NO:3228, the mature soluble polypeptide of SEQ ID NO:3228, e.g., amino acids 134-285 of SEQ ID NO:3228, the extracellular domain of SEQ ID NO:3228, amino acid residues 73-285 of SEQ ID NO:3228 minus the intracellular and transmembrane domains, as well as polypeptides which have at least 80%, 85%, 90% similarity, more preferably at least 95% similarity, and still more preferably at least 96%, 97%, 98% or 99% similarity to those described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0184] The antibodies of the present invention bind BLyS polypeptides including the complete polypeptide encoded by the deposited cDNA including the intracellular, transmembrane and extracellular domains of the polypeptide encoded by the deposited cDNA (ATCC Deposit No. 203518), the mature soluble polypeptide encoded by the deposited cDNA, the extracellular domain minus the intracellular and transmembrane

domains of the protein, the complete polypeptide of SEQ ID NO:3229, the mature soluble of SEQ ID NO:3229, e.g., amino acid residues 134-266 of SEQ ID NO:3229, the extracellular domain of SEQ ID NO:3229, e.g., amino acid residues 73-266 of SEQ ID NO:3229 minus the intracellular and transmembrane domains, as well as polypeptides which have at least 80%, 85%, 90% similarity, more preferably at least 95% similarity, and still more preferably at least 96%, 97%, 98% or 99% similarity to those described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0185] Further antibodies of the present invention bind polypeptides ineluding polypeptides at least 80%, or at least 85% identical, more preferably at least 90% or 95% identical, still more preferably at least 96%, 97%, 98% or 99% identical to the polypeptide encoded by the deposited cDNA (ATCC Deposit No. 97768) or to the polypeptide of SEQ ID NO:3228, and also include antibodies that bind portions of such polypeptides with at least 30 amino acids and more preferably at least 50 amino acids.

[0186] Further antibodies of the present invention bind polypeptides including polypeptides at least 80%, or at least 85% identical, more preferably at least 90% or 95% identical, still more preferably at least 96%, 97%, 98% or 99% identical to the polypeptide encoded by the deposited cDNA (ATCC Deposit No. 203518) or to the polypeptide of SEQ ID NO:3229, and also include antibodies that bind portions of such polypeptides with at least 30 amino acids and more preferably at least 50 amino acids. Polynucleotides eneoding these polypeptides are also encompassed by the invention.

[0187] By "% similarity" for two polypeptides is intended a similarity score produced by comparing the amino acid sequences of the two polypeptides using the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711) and the default settings for determining similarity. Bestfit uses the local homology algorithm of Smith and Waterman (Advances in Applied Mathematics 2:482-489, 1981) to find the best segment of similarity between two sequences.

[0188] By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a reference amino acid sequence of a BLyS polypeptide is intended that the amino acid sequence of the polypeptide is identical to the reference sequence except that the polypeptide sequence may include up to five amino acid alterations per each 100

amino acids of the reference amino acid of the BLyS polypeptide. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a reference amino acid sequence, up to 5% of the amino acid residues in the reference sequence may be deleted or substituted with another amino acid, or a number of amino acids up to 5% of the total amino acid residues in the reference sequence may be inserted into the reference sequence. These alterations of the referenee sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

[0189] As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instanee, the amino acid sequence of SEQ ID NO:3228, the amino acid sequence encoded by the deposited cDNA clone HNEDU15 (ATCC Accession No. 97768), or fragments thereof, or, for instance, to the amino acid sequence of SEQ ID NO:3229, the amino acid sequence encoded by the deposited cDNA clone HDPMC52 (ATCC Accession No. 203518), or fragments thereof, can be determined conventionally using known computer programs such the Bestfit program (Wiseonsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711). When using Bestfit or any other sequence alignment program to determine whether a particular sequence is, for instance, 95% identical to a reference sequence according to the present invention, the parameters are set, of course, such that the percentage of identity is calculated over the full length of the reference amino acid sequence and that gaps in homology of up to 5% of the total number of amino acid residues in the reference sequence are allowed.

[0190] In a specific embodiment, the identity between a reference (query) sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, is determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245 (1990)). Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

According to this embodiment, if the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction is made to the results to take into consideration the fact that the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. A determination of whether a residue is matehed/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of this embodiment. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence. For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matehing/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C-termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are made for the purposes of this embodiment.

Antibodies that Immunospecifically bind BLyS Polypeptides

[0191] The present invention also encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to BLyS polypeptides, which antibodies comprise, or alternatively consist of, all or a portion of a heavy and/or light chain variable domain of the scFvs referred to in Table 1.

[0192] The present invention also encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders assoeiated with aberrant BLyS or BLyS receptor expression or inappropriate BLyS or BLyS reeeptor function in an animal, preferably a mammal, and most preferably a human, comprising using antibodies (ineluding molecules which comprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically bind to BLyS. Diseases and disorders which can be detected, diagnosed or prognosed with the antibodies of the invention include, but are not limited to, immune disorders (*e.g.*, lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (*e.g.*, asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (*e.g.*, AIDS), and proliferative disorders (*e.g.*, leukemia, earcinoma, and lymphoma).

[0193] The present invention further encompasses methods and compositions for preventing, treating or ameliorating diseases or disorders associated with aberrant BLyS or BLyS receptor expression or inappropriate BLyS or BLyS receptor function in an animal, preferably a mammal, and most preferably a human, comprising administering to said animal an effective amount of one or more antibodies (including molecules which comprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically bind to BLyS. Diseases and disorders which can be prevented, treated or inhibited by administering an effective amount of one or more antibodies or moleeules of the invention include, but are not limited to, immune disorders (*e.g.*, lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficieney syndrome), inflammatory disorders (*e.g.*, asthma, allergie disorders, and rheumatoid arthritis), infectious diseases (*e.g.*, AIDS), and proliferative disorders (*e.g.*, leukemia, carcinoma, and lymphoma).

<u>Anti-BLyS Antibodies</u>

[0194] The antibodies of the present invention were discovered, in part, using phage display technology. Single chain antibody molecules ("scFvs") displayed on the surface of phage particles were screened to identify those scFvs that immunospecifically bind to BLyS, including the membrane-bound form and soluble form of BLyS. The present invention encompasses the scFvs and portions thereof that were identified to immunospecifically bind to BLyS, including scFvs that immunospecifically bind to the soluble form of BLyS, scFvs that immunospecifically bind to the membrane-bound form of BLyS, and scFvs that immunospecifically bind to both the soluble form and membrane-bound form of BLyS. In particular, the present invention encompasses scFvs comprising, or alternatively consisting of, the amino acid sequence of SEQ ID NOS: 1 - 2128, as referred to in Table 1. Preferably, the scFvs of the present invention comprise, or alternatively consist of, the amino acid sequence of SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908. The scFvs include scFvs that bind to soluble BLyS (e.g., scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1563 - 1880), scFvs that bind to the membrane-bound form of BLyS (e.g., scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1881 - 2128), and scFvs that bind to both the soluble form and the membrane-bound form of BLyS (e.g., scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1 - 1562). Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs, that immunospecifically bind to BLyS are also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

[0195] In one embodiment of the present invention, scFvs that immunospecifically bind to BLyS comprise a polypeptide having the amino acid sequence of any one of the VH domains referred to in Table 1 and/or any one of the VL domains referred to in Table 1. In preferred embodiments, scFvs of the present invention comprise the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention comprise the amino acid sequence of a VH domain and VL domain from different scFvs referred to in Table 1. In another embodiment, scFvs that immunospecifically bind to BLyS, comprise a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs referred to in Table 1 and/or any one, two, three, or more of the VL CDRs referred to in Table 1. In

preferred embodiments, scFvs of the present invention comprise the amino acid sequence of a VH CDR and VL CDR from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention comprise the amino acid sequence of a VH CDR and VL CDR from different scFvs referred to in Table 1. Molecules comprising, or alternatively consisting of, antibody fragments or variants of the scFvs referred to in Table 1 that immunospecifically bind to BLyS are also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

[0196] (Table 1 can be found at the end of the specification just prior to the claims.)

[0197] In another embodiment of the present invention, an seFv that immunospeeifically binds to a soluble form of BLyS, comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1563 – 1880 as referred to in Table 1. In a preferred embodiment, an scFv that immunospecifically binds to a soluble form of BLyS comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1570 - 1595. In an even more preferred embodiment, an scFv that immunospecifically binds to a soluble form of BLyS comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1563 - 1569.

[0198] In another embodiment of the present invention, an scFv that immunospeeifically binds to a membrane-bound form of BLyS comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1881 - 2128 as referred to in Table 1. In a preferred embodiment, an scFv that immunospecifically binds to a membrane-bound form of BLyS comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1886 - 1908. In an even more preferred embodiment, an scFv that immunospecifically binds to a membrane-bound form of BLyS comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1881 - 1885.

[0199] In another embodiment of the present invention, an scFv that immunospecifically binds to both the soluble form and membrane-bound form of BLyS comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1 - 1562 as referred to in Table 1. In a preferred embodiment, an scFv that immunospecifically binds to both the soluble form and membrane-bound form of BLyS comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:834 - 872. In another

preferred embodiment, an scFv that immunospecifically binds to both the soluble form and membrane-bound form of BLyS comprises, or alternatively consists of, any one of the amino acids sequences of SEQ ID NOS:1 – 46 or 321 - 329. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs, that immunospecifically bind to the soluble form of BLyS and/or the membrane-bound form of BLyS are also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

[0200] In another embodiment of the present invention, scFvs that immunospecifically bind to the soluble form of BLyS, comprise a polypeptide having the amino acid sequence of any one of the VH domains contained in SEQ ID NOS:1563 – 1880 as disclosed in Table 1 and/or any one of the VL domains contained in SEQ ID NOS:1563 - 1880 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of BLyS, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of BLyS, comprise a polypeptide having amino acid sequence of a VH CDR and VL CDR from different scFvs referred to in Table 1. In another embodiment, scFvs that immunospecifically bind to the soluble form of BLyS, comprise a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs SEQ ID NOS:1563 - 1880 as disclosed in Table 1 and/or any one, two, three, or more of the VL CDRs contained in contained SEQ ID NOS:1563 - 1880, as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of BLyS, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of BLyS, comprise a polypeptide having the of the amino acid sequence of a VH domain and VL domain from different scFvs referred to in Table 1. In a preferred embodiment, scFvs that immunospecifically bind to the soluble form of BLyS, comprise a polypeptide having the amino acid sequence of any one of the VH CDR3s contained in SEQ ID NOS:1563 - 1880 as disclosed in Table 1 and/or any one of the VL CDR3s contained in SEQ ID NOS: 1563 - 1880 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to

the soluble form of BLyS, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of BLyS, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from different scFvs referred to in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs, that immunospecifically bind to BLyS, preferably the soluble form of BLyS, are also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

[0201] In another embodiment of the present invention, scFvs that immunospecifically bind to the membrane-bound form of BLyS comprise a polypeptide having the amino acid sequence of any one of the VH domains contained in SEQ ID NOS:1881 - 2128 as disclosed in Table 1 and/or any one of the VL domains contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of BLyS, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from the same scFv referred to in Table 1. In alternative embodiments, seFvs of the present invention that immunospecifically bind to the membrane-bound form of BLyS, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from different scFvs referred to in Table 1. In another embodiment, scFvs that immunospecifically bind to the membrane-bound form of BLyS, comprise a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1 and/or any one, two, three, or more of the VL CDRs contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the membrane-bound form of BLyS, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the membrane-bound form of BLyS, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from different scFvs referred to in Table 1. In a preferred embodiment, scFvs that immunospecifically bind to the membrane-bound form of BLyS, comprise a polypeptide having the amino acid sequenee of any one of the VH CDR3s contained in SEQ ID NOS:

1881 - 2128 as diselosed in Table 1 and/or any one of the VL CDR3s contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the membrane-bound form of BLyS, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the membrane-bound form of BLyS, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from different scFvs referred to in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs, that immunospeeifically bind to BLyS, preferably the membrane-bound form of BLyS, are also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

[0202] In another embodiment of the present invention, scFvs that immunospecifically bind to the soluble form and membrane-bound form of BLyS, comprise a polypeptide having the amino acid sequence of any one of the VH domains contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1 and/or any one of the VL domains contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble and membrane-bound forms of BLyS, comprise a polypeptide having the amino acid sequenee of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the soluble form and membrane-bound form of BLyS, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from different scFvs referred to in Table 1. In another embodiment, scFvs that immunospecifically bind to the soluble form and membrane-bound form of BLyS comprise a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1 and/or any one, two, three, or more of the VL CDRs contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble form and membrane-bound form of BLyS, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the soluble and membrane-bound forms of BLyS, comprise a polypeptide having the amino acid sequence of a VH domain and VL

domain from different scFvs referred to in Table 1. In a preferred embodiment, scFvs that immunospecifically bind to the soluble and membrane-bound forms of BLyS, comprise a polypeptide having the amino acid sequence of any one of the VH CDR3s contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1 and/or any one of the VL CDR3s contained in SEQ ID NOS:1 - 1562, as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble and membrane-bound forms of BLyS, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the soluble and membrane-bound forms of BLyS, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from different scFvs referred to in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs or molecules, that immunospecifically bind to BLyS, preferably the soluble and membrane-bound forms of BLyS, are also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

[0203] The present invention provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or a polypeptide fragment of BLyS. In particular, the invention provides antibodies corresponding to the scFvs referred to in Table 1, such scFvs may routinely be "converted" to immunoglobulin molecules by inserting, for example, the nucleotide sequences encoding the VH and/or VL domains of the scFv into an expression vector containing the constant domain sequences and engineered to direct the expression of the immunoglobulin molecule, as described in more detail in Example 20, *infra*.

[0204] In one embodiment, the invention provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) wherein said antibodies comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one of the VH domains contained in the sequences referred to in Table 1. The present invention also provides antibodies that immunospecifically bind to a polypeptide, or polypeptide fragment of BLyS, wherein said antibodies comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one, two, three, or more of the VH CDRs contained in the sequences referred to in Table 1.

Molecules comprising, or alternatively consisting of, these antibodies, or antibody fragments or variants thereof, that immunospecifically bind to BLyS or a BLyS fragment are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments and/or variants.

[0205] In one embodiment of the present invention, antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind BLyS, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VH CDR referred to in Table 1. In partieular, the invention provides antibodies that immunospecifically bind BLyS, comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of a VH CDR1 contained in SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, or 1881 – 1885 as disclosed in Table 1. In another embodiment, antibodies that immunospecifically bind BLyS, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VH CDR2 contained in SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, or 1881 – 1885 as diselosed in Table 1. In a preferred embodiment, antibodies that immunospecifically bind BLyS, comprise, or alternatively consist of a polypeptide having the amino acid sequence of a VH CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, or 1881 – 1885 as diselosed in Table 1. In yet another embodiment, antibodies that immunospecifically bind BLyS, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VH CDR1 contained in SEQ ID NOS:834 - 872, 1570 - 1595, or 1886 – 1908 as disclosed in Table 1; a VH CDR2 eontained in SEQ ID NOS: SEQ ID NOS: SEQ ID NOS:834 - 872, 1570 - 1595, or 1886 – 1908; and/or a VH CDR3 contained in SEQ ID NOS: SEQ ID NOS:834 - 872, 1570 - 1595, or 1886 – 1908 as disclosed in Table 1. Preferably, antibodies of the invention comprise, or alternatively consist of, VH CDRs that are derived from the same scFv as disclosed in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies that immunospecifically bind to BLyS are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments or variants.

[0206] The present invention provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants) that immunospecifically bind to a polypeptide, or polypeptide fragment of BLyS. In particular, the invention provides antibodies wherein said antibodies comprise, or alternatively consist of, a VL domain

having an amino acid sequence of any one of the VL domains referred to in Table 1. The present invention also provides antibodies that immunospecifically bind to a polypeptide or polypeptide fragment of BLyS, wherein said antibodies comprise, or alternatively consist of, a VL CDR having an amino acid sequence of any one, two, three, or more of the VL CDRs contained in the sequences referred to in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies that immunospecifically bind to BLyS are also eneompassed by the invention, as are nucleic acid molecules encoding these antibodies, moleeules, fragments or variants.

[0207] In one embodiment of the present invention, antibodies (ineluding molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind BLyS, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VL CDR referred to in Table 1. In particular, the invention provides antibodies that immunospecifically bind BLyS, eomprising, or alternatively consisting of, a polypeptide having the amino acid sequenee of a VL CDR1 eontained in SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, or 1881 – 1885 as disclosed in Table 1. In another embodiment, antibodies that immunospecifically bind BLyS eomprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VL CDR2 contained in SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, or 1881 – 1885 as disclosed in Table 1. In a preferred embodiment, antibodies comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VL CDR3 eontained in SEQ ID NOS: in SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, or 1881 – 1885 disclosed in Table 1. In yet another embodiment, antibodies that immnospecifically bind BLyS comprise, or alternatively consist of: a polypeptide having the amino acid sequenee of a VL CDR1 contained in SEQ ID NOS:834 - 872, 1570 - 1595, or 1886 – 1908 as disclosed in Table 1; a VL CDR2 SEQ ID NOS :834 - 872, 1570 - 1595, or 1886 – 1908 as disclosed in Table 1; and a VL CDR3 contained SEQ ID NOS:834 - 872, 1570 - 1595, or 1886 – 1908 as diselosed in Table 1. Preferably, antibodies of the invention comprise, or alternatively consist of, VL CDRs that are derived from the same scFv as disclosed in Table 1. Molecules eomprising, or alternatively consisting of, fragments or variants of these antibodies, that immunospeeifically bind to BLyS are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments or variants.

[0208] The present invention also provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or a polypeptide fragment of BLyS, wherein said antibodies comprise, or alternatively consist of, a VH domain of one of the scFvs referred to in Table 1 combined with a VL domain of one of the scFvs referred to in Table 1, or other VL domain. The present invention further provides antibodies (including molecules comprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or a polypeptide fragment of BLyS, wherein said antibodies comprise, or alternatively consist of, a VL domain of one of the scFvs referred to in Table 1 combined with a VH domain of one of the scFvs referred to in Table 1, or other VH domain. In a preferred embodiment, antibodies that immunospecifically bind to a polypeptide or a polypeptide fragment of BLyS, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VH domain contained SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1 and a VL domain contained in contained SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1. In a further preferred embodiment, the antibodies of the invention comprise, or alternatively consist of, a VH and a VL domain from the same scFv as disclosed in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies, that immunospecifically bind to BLyS are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments or variants.

[0209] The present invention also provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants) that immunospecifically bind to a polypeptide or polypeptide fragment of BLyS, wherein said antibodies comprise, or alternatively consist of, one, two, three, or more VH CDRs and one, two, three or more VL CDRs, as referred to in Table 1. In particular, the invention provides for antibodies that immunospecifically bind to a polypeptide or polypeptide fragment of BLyS, wherein said antibodies comprise, or alternatively consist of, a VH CDR1 and a VL CDR1, a VH CDR1 and a VL CDR2, a VH CDR1 and a VL CDR3, a VH CDR2 and a VL CDR1, VH CDR2 and VL CDR2, a VH CDR2 and a VL CDR3, a VH CDR3 and a VH CDR1, a VH CDR3 and a VL CDR2, a VH CDR3 and a VL CDR3, or any combination thereof, of the VH CDRs and VL CDRs referred to in Table 1. In a

preferred embodiment, one or more of these combinations are from the same scFv as disclosed in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies, that immunospecifically bind to BLyS are also encompassed by the invention, as are nucleie acid molecules encoding these antibodies, molecules, fragments or variants.

[0210] In a preferred embodiment the invention provides antibodies wherein the VH CDRX (where X=1, 2, or 3) and VL CDRY (where Y= 1, 2, or 3) are from scFvs with the same specificity (i.e., from scFvs that bind soluble BLyS, from seFvs that bind membrane-bound BLyS, or from scFvs that bind both soluble and membrane-bound BLyS. Molecules comprising, or alternatively eonsisting of, fragments or variants of these antibodies, that immunospecifically bind to BLyS are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments or variants.

[0211] The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin moleeules, *i.e.*, molecules that contain an antigen binding site that immunospecifically binds an antigen. As such, the term "antibody" encompasses not only whole antibody molecules, but also antibody fragments, as well as variants (including derivatives) of antibodies and antibody fragments. Antibodies of the invention include, but are not limited to, monoclonal, multispecific, human or chimeric antibodies, single chain antibodies, single chain Fvs (scFvs), Fab fragments, $F(ab')_2$ fragments, Fd fragments, disulfide-linked Fvs (sdFvs), antiidiotypic (anti-Id) antibodies (including, *e.g.*, anti-Id antibodies to antibodies of the invention), and epitope-binding fragments of any of the above. The immunoglobulin molecules of the invention can be of any type (*e.g.*, IgG, IgE, IgM, IgD, IgA and IgY), class (*e.g.*, IgG_1, IgG_2, IgG_3, IgG_4, IgA_1 and IgA_2) or subclass of immunoglobulin molecule. The antibodies of the present invention also include molecules comprising, or alternatively consisting of, a polypeptide having an amino acid sequence of a portion of an amino acid sequence contained SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908. Preferably, an antibody of the invention comprises, or alternatively consists of, a polypeptide having an amino acid sequence of a VH domain, VH CDR, VL domain, or VL CDR of any one those contained in the sequences referred to in Table 1. Antibodies of the invention also include molecules eomprising, or alternatively consisting of, fragments or variants of the above antibodies that immunospecifically bind BLyS.

[0212] Most preferably the antibodies of the present invention are whole antibodies or antibody fragments that immunospecifically bind human BLyS. Antibody fragments of the invention that immunospeeifically bind human BLyS include, but are not limited to, Fab, Fab' and $F(ab')_2$, Fd fragments, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFvs), fragments eomprising, or alternatively consisting of, either a VL or VH domain, and epitope binding fragments of any of the above.

[0213] BLyS-binding antibody fragments, including single-chain antibodies, may comprise, or alternatively consist of, the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains. In a preferred embodiment, the antibodies of the invention comprise, or alternatively consist of, a polypeptide that immunospecifically binds to BLyS, said polypeptides comprise, or alternatively consist of, one, two, three, four, five, six or more CDRs referred to in Table 1, preferably a polypeptide having an amino acid sequence of a VH CDR3 and/or a VL CDR3 of contained SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1. Most preferably, antibodies of the invention comprise, or alternatively consist of, one, two, three, four, five, six or more CDRs from the same scFv, as referred to in Table 1. The antibodies of the invention may be from any animal origin, including birds and mammals. Preferably, the antibodies are human, murine (*e.g.*, mouse and rat), donkey, sheep, rabbit, goat, guinea pig, camel, horse, or chicken. Most preferably, the antibodies are human antibodies. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and inelude antibodies isolated from human immunoglobulin libraries and xenomice or other organisms that have been genetically engineered to produce human antibodies. For a detailed discussion of a few of the technologies for producing human antibodies and human monoelonal antibodies and protocols for producing such antibodies, see, e.g., PCT publieations WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European Patent No. 0 598 877; U.S. Patent Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; 5,885,793; 5,916,771; and 5,939,598; and Lonberg and Huszar, Int. Rev. Immunol. 13:65-93 (1995), which are incorporated by reference herein in their entirety. Human antibodies or "humanized" chimeric monoclonal antibodies can be produced using techniques described herein or otherwise known in the art. For example, methods for produeing chimeric antibodies are known in the art. See, for review

the following references which are hereby incorporated in their entirety: Morrison, *Science 229*:1202 (1985); Oi et al., *BioTechniques 4*:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne *et al., Nature 312*:643 (1984); Neuberger *et al., Nature 314*:268 (1985). In addition, eompanies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

[0214] The antibodies of the present invention may be monovalent, bivalent, trivalent or multivalent. For example, monovalent scFvs can be multimerized either chemically or by assoeiation with another protein or substance. An scFv that is fused to a hexahistidine tag or a Flag tag can be multimerized using Ni-NTA agarose (Qiagen) or using anti-Flag antibodies (Stratagene, Inc.).

[0215] The antibodies of the present invention may be monospecific, bispeeific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of a BLyS polypeptide, or fragment thereof, or may be specific for both a BLyS polypeptide, or fragment thereof, and a heterologous epitope, such as a heterologous polypeptide or solid support material. See, *e.g.*, PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, *et al.*, J. Immunol. 147:60-69 (1991); U.S. Patent Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny *et al.*, J. Immunol. 148:1547-1553 (1992).

[0216] The antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may bind immunospecifically to murine BLyS (e.g., a polypeptide having the amino acid sequence of human BLyS (SEQ ID NOS:3228 and/or 3229) or BLyS expressed on human monocytes; murine BLyS (SEQ ID NOS:3230 and/or 3231) or BLyS expressed on murine monocytes; rat BLyS (either the soluble forms as given in SEQ ID NOS:3232, 3233, 3234 and/or 3235 or in a membrane associated form, *e.g.*, on the surface of rat monocytes); or monkey BLyS (e.g., the monkey BLyS polypeptides of SEQ ID NOS:3236 and/or 3237, the soluble form of monkey BLyS, or BLyS expressed on monkey monocytes), preferably the antibodies of the invention bind immunospecifically to human BLyS. Preferably, the antibodies of the invention bind immunospecifically to human and monkey BLyS. Also

preferably, the antibodies of the invention bind immunospecifically to human BLyS and murine BLyS. More preferably, antibodies of the invention, bind immunospecifically and with higher affinity to human BLyS than to murine BLyS.

[0217] Antibodies of the present invention may also be described or specified in terms of their cross-reactivity. Antibodies that do not bind any other analog, ortholog, or homolog of a polypeptide of the present invention are included. Antibodies that bind polypeptides with at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, and at least 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In a specific embodiment, antibodies of the present invention cross react with APRIL (SEQ ID NO:3239; GenBank Accession No. AF046888; J. Exp. Med. 188(6):1185-1190; PCT International Publication WO97/33902). In specific embodiments, antibodies of the present invention cross-react with murine, rat and/or rabbit homologs of human proteins and the corresponding epitopes thereof. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In a specific embodiment, the above-described cross-reactivity is with respect to any single specific antigenic or immunogenic polypeptide, or combination(s) of 2, 3, 4, 5, or more of the specific antigenic and/or immunogenic polypeptides disclosed herein. Further included in the present invention are antibodies which bind polypeptides encoded by polynucleotides which hybridize to a polynucleotide of the present invention under hybridization conditions (as described herein).

[0218] In a specific embodiment, antibodies of the present invention cross react with APRIL (SEQ ID NO:3239; GenBank Accession No. AF046888; J. Exp. Med. 188(6):1185-1190; PCT International Publication WO97/33902). In specific embodiments, antibodies that immunospecifically bind both BLyS and APRIL comprise all or a portion the BAB2001, BAB2080, BAB2015, BAB2019, BAB2087, BAB2016, BAB2034 or BAB2065 scFVs (SEQ ID NOS:3240-3247). These scFvs were isolated by panning a phage scFv library comprising VH and VL domains obtained from human bone marrow B cells (BM library). Phage from the BM phage library were first selected for

binding to soluble BLyS (amino acids 134-285 of SEQ ID NO:3228). A second round of selection for binding to the soluble form of APRIL (amino acids 105-250 of SEQ ID NO:3239) was then performed on the BLyS binding phage selected in round one. A third round of selection for binding to the soluble form of APRIL (amino acids 105-250 of SEQ ID NO:3239) was then performed on the phage selected in round two. A final (fourth) round of selection for binding to the soluble form of BLyS (amino acids 134-285 of SEQ ID NO:3228) was then performed on the phage selected in round three. Phage clones that bound BLyS in the fourth round of selection were eluted with either 0.1M triethylamine (TEA) or with a TACI-Fc fusion protein (e.g., the extracellular domain of TACI (amino acids 31 to 159 of Genbank Accession No. AAC51790) fused to Fc). Eluted Phage were collected and sequenced (SEQ ID NOS:3240-3247). Of 79 sequences, there were 8 unique sequences (SEQ ID NOS:3240-3247).

[0219] Isolated scFv clones (e.g., scFvs corresponding to SEQ ID NOS:3240-3247 or other scFvs described in Table 1) or antibodies comprising at least a portion of said scFV clones may be screened for their ability to bind their ability to bind the soluble form of BLyS and the soluble form of APRIL by ELISA. Isolated scFv clones or antibodies eomprising at least a portion of said seFv clones may also be screened for their ability to inhibit binding of a soluble form of BLyS or BLyS heterotrimer to TACI, BCMA or BAFF-R (Genbank Accession Nos. AAC51790, NP_00183, and NP_443177, respectively). Isolated scFv clones or antibodies comprising at least a portion of said scFV clones may also be screened for their ability to inhibit BLyS or BLyS heterotrimer mediated biologieal activities (e.g. stimulation of B cell proliferation and/or stimulation of immunoglobulin production).

[0220] In specifie embodiments, antibodies that immunospecifically bind both BLyS and APRIL comprise all or a portion (e.g., VHCDR, VLCDR, VH domain, VL domain) of the BAB2001, BAB2015, BAB2016, BAB2019, BAB2034, BAB2065, or BAB2080 scFVs (SEQ ID NOS:3240-3247).

[0221] In preferred embodiments, the antibodies of the present invention (including molecules comprising, or alternatively eonsisting of, antibody fragments or variants thereof), immunospecifically bind to BLyS and do not cross-react with any other antigens. In more preferred embodiments, the antibodies of the invention immunopecifically bind to

BLyS and do not eross-react with TRAIL, APRIL, Endokine-alpha, TNF-alpha, TNF-beta, Fas-L or LIGHT.

[0222] The present invention also provides for a nucleic acid molecule, generally isolated, encoding an antibody of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof). In one embodiment, a nucleie acid moleeule of the invention encodes an antibody comprising, or alternatively consisting of, a VH domain having an amino acid sequence of any one of the VH domains referred to in Table 1. In another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VH CDR1 having an amino acid sequence of any one of the VH CDR1s referred to in Table 1. In another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VH CDR2 having an amino acid sequence of any one of the VH CDR2s referred to in Table 1. In yet another embodiment, a nucleie acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VH CDR3 having an amino acid sequence of any one of the VH CDR3s referred to in Table 1. Nucleic acid molecules encoding antibodies that immunospecifically bind BLyS and comprise, or alternatively consist of, fragments or variants of the VH domains and/or VH CDRs are also encompassed by the invention.

[0223] In another embodiment, a nucleie acid moleeule of the invention encodes an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), comprising, or alternatively consisting of, a VL domain having an amino acid sequence of any one of the VL domains referred to in Table 1. In another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VL CDR1 having amino acid sequence of any one of the VL CDR1s referred to in Table 1. In another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VL CDR2 having an amino aeid sequence of any one of the VL CDR2s referred to in Table 1. In yet another embodiment, a nucleie acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VL CDR3 having an amino acid sequence of any one of the VL CDR3s referred to in Table 1. Nucleic acid encoding antibodies that immunospecifically bind BLyS and comprise, or

alternatively consist of, fragments or variants of the VL domains and/or VLCDR(s) are also encompassed by the invention.

[0224] In another embodiment, a nucleic acid molecule of the invention encodes an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), comprising, or alternatively consisting of, a VH domain having an amino acid sequence of any one of the VH domains referred to in Table 1 and a VL domain having an amino acid sequence of any one of the VL domains referred to in Table 1. In another embodiment, a nucleic acid molecule of the invention encodes an antibody comprising, or alternatively consisting of, a VH CDR1, a VL CDR1, a VH CDR2, a VL CDR2, a VH CDR3, a VL CDR3, or any combination thereof having an amino acid sequence referred to in Table 1. Nucleic acid encoding antibodies that immunospecifically bind BLyS and comprise, or alternatively consist of, fragments or variants of the VL and/or domains and/or VHCDR(s) and/or VLCDR(s) are also encompassed by the invention.

[0225] The present invention also provides antibodies that comprise, or alternatively consist of, variants (including derivatives) of the VH domains, VH CDRs, VL domains, and VL CDRs described herein, which antibodies immunospecifically bind to BLyS. Standard techniques known to those of skill in the art can be used to introduce mutations in the nucleotide sequence encoding a molecule of the invention, ineluding, for example, site-directed mutagenesis and PCR-mediated mutagenesis which result in amino acid substitutions. Preferably, the variants (including derivatives) encode less than 50 amino acid substitutions, less than 40 amino acid subsitutions, less than 30 amino acid substitutions, less than 25 amino acid substitutions, less than 20 amino acid substitutions, less than 15 amino acid substitutions, less than 10 amino acid substitutions, less than 5 amino acid substitutions, less than 4 amino acid substitutions, less than 3 amino acid substitutions, or less than 2 amino acid substitutions relative to the reference VH domain, VHCDR1, VHCDR2, VHCDR3, VL domain, VLCDR1, VLCDR2, or VLCDR3. In specific embodiments, the variants eneode substitutions of VHCDR3. In a preferred embodiment, the variants have conservative amino acid substitutions at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a side chain with a similar charge. Families of amino acid residues having side chains with

similar charges have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Alternatively, mutations can be introduced randomly along all or part of the coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for biological activity to identify mutants that retain activity (e.g., the ability to bind BLyS). Following mutagenesis, the encoded protein may routinely be expressed and the functional and/or biological activity of the encoded protein, (e.g., ability to immunospecifically bind BLyS) can be determined using techniques described herein or by routinely modifying techniques known in the art.

[0226] The antibodies of the invention include derivatives (i.e., variants) that are modified, e.g., by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not affect the ability of the antibody to immunospecifically bind to BLyS. For example, but not by way of limitation, derivatives of the invention include antibodies that have been modified, *e.g.*, by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to, specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, ete. Additionally, the derivative may contain one or more non-classical amino acids.

[0227] In a specific embodiment, an antibody of the invention (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof), that immunospecifically binds BLyS, comprises, or alternatively consists of, an amino acid sequence encoded by a nucleotide sequenee that hybridizes to a nucleotide sequence that is complementary to that encoding one of the VH or VL domains referred to in Table 1 under stringent conditions, *e.g.*, hybridization to filter-bound DNA in 6x sodium chloride/sodium citrate (SSC) at about 45° C followed by one or more washes in 0.2xSSC/0.1% SDS at about 50-65° C, under highly stringent conditions, *e.g.*,

hybridization to filter-bound nucleic acid in 6xSSC at about 45° C followed by one or more washes in 0.1xSSC/0.2% SDS at about 68° C, or under other stringent hybridization conditions which are known to those of skill in the art (see, for example, Ausubel, F.M. et al., eds. , 1989, *Current Protocols in Molecular Biology*, Vol. I, Green Publishing Associates, Inc. and John Wiley & Sons, Inc., New York at pages 6.3.1-6.3.6 and 2.10.3). In another embodiment, an antibody of the invention that immunospecifically binds to BLyS, comprises, or alternatively consists of, an amino acid sequence encoded by a nucleotide sequence that hybridizes to a nucleotide sequence that is complementary to that encoding one of the VH CDRs or VL CDRs referred to in Table 1 under stringent conditions, *e.g.*, hybridization under conditions as described above, or under other stringent hybridization conditions which are known to those of skill in the art. In another embodiment, an antibody of the invention that immunospecifically binds to BLyS, comprises, or alternatively consists of, an amino acid sequence encoded by a nucleotide sequence that hybridizes to a nucleotide sequence that is complementary to that encoding one of the VH CDR3s referred to in Table 1 under stringent conditions *e.g.*, hybridization under conditions as described above, or under other stringent hybridization conditions which are known to those of skill in the art. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0228] In another embodiment, an antibody (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof), that immunospecifically binds to BLyS comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to any one of the VH domains referred to in Table 1. In another embodiment, an antibody of the invention that immunospecifically binds to BLyS comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to any one of the VH CDRs referred to in Table 1. In another embodiment, an antibody of the invention that immunospecifically binds to BLyS comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least

50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to any one of the VH CDR3s referred to in Table 1. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0229] In another embodiment, an antibody of the invention (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof), that immunospecifically binds to BLyS eomprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to any one of the VL domains referred to in Table 1. In another embodiment, an antibody of the invention that immunospecifically binds to BLyS comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to any one of the VL CDRs referred to in Table 1. In another embodiment, an antibody of the invention that immunospecifically binds to BLyS comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to any one of the VL CDR3s referred to in Table 1. Nucleic acid molecules encoding these antibodies are also eneompassed by the invention.

[0230] Antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may also be described or specified in terms of their binding affinity for to BLyS polypeptides or fragments or variants of BLyS polypeptides (e.g., to the soluble form of BLyS and/or membrane-bound form of BLyS). In specific embodiments, antibodies of the invention bind BLyS polypeptides, or fragments or variants thereof, with a dissociation eonstant or K_D of less than or equal to $5 X 10^{-2}$ M, 10^{-2} M, $5 X 10^{-3}$ M, 10^{-3} M, $5 X 10^{-4}$ M, 10^{-4} M, $5 X 10^{-5}$ M, or 10^{-5} M. More preferably, antibodies of the invention bind BLyS polypeptides or fragments or variants thereof with a dissociation constant or K_D less than or equal to $5 X 10^{-6}$ M, 10^{-6} M, $5 X 10^{-7}$ M, 10^{-7} M, $5 X 10^{-8}$ M, or 10^{-8} M. Even more preferably,

antibodies of the invention bind BLyS polypeptides or fragments or variants thereof with a dissoeiation constant or K_D less than or equal to 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12} M, 10^{-12} M, $5 \times {}^{-13}$ M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, or 10^{-15} M. The invention encompasses antibodies that bind BLyS polypeptides with a dissociation constant or K_D that is within any one of the ranges that are between each of the individual recited values.

[0231] In speeific embodiments, antibodies of the invention bind BLyS polypeptides or fragments or variants thereof with an off rate (k_{off}) of less than or equal to 5×10^{-2} sec^{-1}, 10^{-2} sec^{-1}, 5×10^{-3} sec^{-1} or 10^{-3} sec^{-1}. More preferably, antibodies of the invention bind BLyS polypeptides or fragments or variants thereof with an off rate (k_{off}) less than or equal to 5×10^{-4} sec^{-1}, 10^{-4} sec^{-1}, 5×10^{-5} sec^{-1}, or 10^{-5} sec^{-1} 5×10^{-6} sec^{-1}, 10^{-6} sec^{-1}, 5×10^{-7} sec^{-1} or 10^{-7} sec^{-1}. The invention encompasses antibodies that bind BLyS polypeptides with an off rate (k_{off}) that is within any one of the ranges that are between each of the individual recited values.

[0232] In other embodiments, antibodies of the invention bind BLyS polypeptides or fragments or variants thereof with an on rate (k_{on}) of greater than or equal to 10^3 M^{-1} sec^{-1}, 5×10^3 M^{-1} sec^{-1}, 10^4 M^{-1} sec^{-1} or 5×10^4 M^{-1} sec^{-1}. More preferably, antibodies of the invention bind BLyS polypeptides or fragments or variants thereof with an on rate (k_{on}) greater than or equal to 10^5 M^{-1} sec^{-1}, 5×10^5 M^{-1} sec^{-1}, 10^6 M^{-1} see-1, or 5×10^6 M^{-1} sec^{-1} or 10^7 M^{-1} sec^{-1}. The invention encompasses antibodies that bind BLyS polypeptides with on rate (k_{on}) that is within any one of the ranges that are between each of the individual recited values.

[0233] The invention also eneompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that have one or more of the same biological characteristics as one or more of the antibodies described herein. By "biological characteristics" is meant, the in vitro or in vivo activities or properties of the antibodies, such as, for example, the ability to bind to BLyS (e.g., the soluble form of BLyS, the membrane-bound form of BLyS, the soluble form and membrane-bound form of BLyS), and/or an antigenic and/or epitope region of BLyS), the ability to substantially block BLyS/BLyS receptor (e.g., TACI - GenBank accession number AAC51790; BCMA - GenBank accession number NP_001183; and/or BAFF-R - GenBank accession number NP_443177) binding, or the ability to block BLyS mediated

biological activity (e.g., stimulation of B cell proliferation and immunoglobulin production). Optionally, the antibodies of the invention will bind to the same epitope as at least one of the antibodies specifically referred to herein. Such epitope binding can be routinely determined using assays known in the art.

[0234] The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that neutralize BLyS or a fragment thereof, said antibodies comprising, or alternatively consisting of, a portion (*i.e.*, a VH domain, VL domain, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, or VL CDR3) of an scFv referred to in Table 1, more preferably having an amino acid sequence contained in SEQ ID NOS:834 - 872, 1570 - 1595, or 1886 – 1908, and even more preferably having an amino acid sequence contained in SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, or 1881 – 1885 as disclosed in Table 1, or a fragment or variant thereof. By an antibody that "neutralizes BLyS or a fragment thereof" is meant an antibody that diminishes or abolishes the ability of BLyS to bind to its receptor (e.g., TACI - GenBank accession number AAC51790; BCMA - GenBank accession number NP_001183; and/or BAFF-R - GenBank accession number NP_443177) to stimulate B cell proliferation, to stimulate immunoglobulin secretion by B cells, and/or to stimulate the BLyS receptor signalling cascade. In one embodiment, an antibody that neutralizes BLyS or a fragment thereof, eomprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as diselosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that neutralizes BLyS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that neutralizes BLyS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR domain in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In a preferred embodiment, an antibody that neutralizes BLyS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or

a fragment or variant thereof. In another embodiment, an antibody that neutralizes BLyS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as diselosed in Table 1, or a fragment or variant thereof. In another preferred embodiment, an antibody that neutralizes BLyS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0235] The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that inhibit (i.e., diminish or abolish) BLyS-mediated B cell proliferation as determined by any method known in the art such as, for example, the assays described in Examples 21 and 22, *infra*, said antibodies comprising, or alternatively eonsisting of, a portion (*e.g.*, a VH domain, VL domain, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, or VL CDR3) of an scFv having an amino acid sequence SEQ ID NOS:834 - 872, 1570 - 1595, 1886 – 1908, and even more preferably having an amino acid sequence SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, 1881 - 1885 as disclosed in Table 1 or a fragment or variant thereof. In one embodiment, an antibody that inhibits BLyS-mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908, as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that inhibits BLyS-mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL domain eontained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In a preferred embodiment, an antibody that inhibits BLyS-mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as diselosed in Table 1, or a fragment or variant thereof. In another preferred embodiment, an antibody that inhibits BLyS-mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR3 contained SEQ ID NOS:1 -

46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0236] The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that inhibit (i.e., diminish or abolish) BLyS-mediated stimulation of B cell survival as determined by any method known in the art such as, for example, the assays described in Examples 21 and 22, *infra*, said antibodies comprising, or alternatively consisting of, a portion (*e.g.*, a VH domain, VL domain, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, or VL CDR3) of an scFv having an amino acid sequence SEQ ID NOS:834 - 872, 1570 - 1595, 1886 – 1908, and even more preferably having an amino acid sequence SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, 1881 - 1885 as disclosed in Table 1 or a fragment or variant thereof. In one embodiment, an antibody that inhibits BLyS-mediated stimulation of B cell survival, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908, as diselosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that inhibits BLyS-mediated stimulation of B cell survival, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In a preferred embodiment, an antibody that inhibits BLyS-mediated stimulation of B cell survival, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In another preferred embodiment, an antibody that inhibits BLyS-mediated stimulation of B cell survival, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR3 contained SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0237] The present invention also provides for antibodies (ineluding molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that inhibit (i.e., diminish or abolish) BLyS-mediated stimulation of B cell differentiation as

determined by any method known in the art such as, for example, the assays described in Examples 21 and 22, *infra*, said antibodies comprising, or alternatively consisting of, a portion (*e.g.*, a VH domain, VL domain, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, or VL CDR3) of an scFv having an amino acid sequence SEQ ID NOS:834 - 872, 1570 - 1595, 1886 – 1908, and even more preferably having an amino acid sequence SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, 1881 - 1885 as disclosed in Table 1 or a fragment or variant thereof. In one embodiment, an antibody that inhibits BLyS-mediated stimulation of B cell differentiation, eomprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908, as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that inhibits BLyS-mediated stimulation of B cell differentiation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In a preferred embodiment, an antibody that inhibits BLyS-mediated stimulation of B cell differentiation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In another preferred embodiment, an antibody that inhibits BLyS-mediated stimulation of B cell differentiation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR3 contained SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0238] The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that inhibit (i.e., diminish or abolish) BLyS-mediated stimulation of immunoglobulin produetion by B cells as determined by any method known in the art sueh as, for example, the assays described in Examples 21 and 22, *infra*, said antibodies comprising, or alternatively consisting of, a portion (*e.g.*, a VH domain, VL domain, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, or VL CDR3) of an scFv having an amino acid sequence SEQ ID NOS:834 - 872, 1570 - 1595, 1886 – 1908, and even more preferably

having an amino acid sequence SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, 1881 - 1885 as disclosed in Table 1 or a fragment or variant thereof. In one embodiment, an antibody that inhibits BLyS-mediated stimulation of immunoglobulin production by B cells, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908, as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that inhibits BLyS-mediated stimulation of immunoglobulin production by B cells, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In a preferred embodiment, an antibody that inhibits BLyS-mediated stimulation of immunoglobulin production by B cells, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In another preferred embodiment, an antibody that inhibits BLyS-mediated stimulation of immunoglobulin production by B cells, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR3 contained SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0239] The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that enhance the activity of BLyS or a fragment thereof, said antibodies comprising, or alternatively consisting of, a portion (*i.e.*, a VH domain, VL domain, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, or VL CDR3) of an scFv having an amino acid sequence SEQ ID NOS:834 - 872, 1570 - 1595, or 1886 – 1908, and preferably having an amino acid sequence of SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, or 1881 – 1885, as disclosed in Table 1, or a fragment or variant thereof. By an antibody that "enhances the activity of BLyS or a fragment thereof" is meant an antibody increases the ability of BLyS to bind to its receptor (e.g., TACI - GenBank accession number AAC51790; BCMA - GenBank accession number NP_001183; and/or BAFF-R - GenBank accession number NP_443177), to stimulate B cell proliferation, to stimulate immunoglobulin secretion by B

cells, and/or to stimulate the BLyS receptor signalling cascade. In one embodiment, an antibody that enhances the activity of BLyS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that enhances the activity of BLyS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as diselosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that enhances the activity of BLyS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In a preferred embodiment, an antibody that enhances the activity of BLyS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that enhances BLyS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino aeid sequence of a VL CDR domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In another preferred embodiment, an antibody that enhances the activity of BLyS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0240] The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that stimulate BLyS-mediated B cell proliferation as determined by any method known in the art, such as, for example, the assays described in Examples 21 and 22, *infra*, said antibodies comprising, or alternatively consisting of, a portion (*e.g.*, a VH domain, VL domain, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, or VL CDR3) of an scFv having an amino acid sequence of SEQ ID NOS:834 - 872, 1570 - 1595, or 1886 –

1908, and even more preferably having an amino acid sequence of SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, or 1881 - 1885 as disclosed in Table 1 or a fragment or variant thereof. In one embodiment, an antibody that stimulates BLyS-mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that stimulates BLyS-mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In a preferred embodiment, an antibody that stimulates BLyS-mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In another preferred embodiment, an antibody that stimulates BLyS-mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0241] The present invention also provides for fusion proteins comprising, or alternatively consisting of, an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that immunospecifically binds to BLyS, and a heterologous polypeptide. Preferably, the heterologous polypeptide to which the antibody is fused to is useful for B-cell function or is useful to target the antibody to B-cells. In an alternative preferred embodiment, the heterologous polypeptide to which the antibody is fused to is useful for monocyte cell function or is useful to target the antibody to a monocyte. In another embodiment, the heterologous polypeptide to which the antibody is fused is albumin (including but not limited to recombinant human serum albumin or fragments or variants thereof (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)). In a preferred embodiment, antibodies of the present invention (including fragments or variants thereof) are fused with the

mature form of human serum albumin (i.e., amino acids 1 – 585 of human serum albumin as shown in Figures 1 and 2 of EP Patent 0 322 094) which is herein incorporated by reference in its entirety. In another preferred embodiment, antibodies of the present invention (including fragments or variants thereof) are fused with polypeptide fragments comprising, or alternatively consisting of, amino acid residues 1-x of human serum albumin, where x is an integer from 1 to 585 and the albumin fragment has human serum albumin activity. In another preferred embodiment, antibodies of the present invention (including fragments or variants thereof) are fused with polypeptide fragments comprising, or alternatively consisting of, amino acid residues 1-z of human serum albumin, where z is an integer from 369 to 419, as described in U.S. Patent 5,766,883 herein incorporated by reference in its entirety. Antibodies of the present invention (including fragments or variants thereof) may be fused to either the N- or C-terminal end of the heterologous protein (e.g., immunoglobulin Fc polypeptide or human serum albumin polypeptide).

[0242] In one embodiment, a fusion protein of the invention comprises, or alternatively consists of, a polypeptide having the amino acid sequence of any one or more of the VH domains referred to in Table 1 or the amino acid sequence of any one or more of the VL domains referred to in Table 1 or fragments or variants thereof, and a heterologous polypeptide sequence. In another embodiment, a fusion protein of the present invention comprises, or alternatively consists of, a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs referred to in Table 1, or the amino acid sequence of any one, two, three, or more of the VL CDRs referred to in Table 1, or fragments or variants thereof, and a heterologous polypeptide sequence. In a preferred embodiment, the fusion protein comprises, or alternatively consists of, a polypeptide having the amino acid sequence of, a VH CDR3 referred to in Table 1, or fragment or variant thereof, and a heterologous polypeptide sequence, which fusion protein immunospecifically binds to BLyS. In another embodiment, a fusion protein comprises, or alternatively consists of a polypeptide having the amino acid sequence of at least one VH domain referred to in Table 1 and the amino acid sequence of at least one VL domain referred to in Table 1 or fragments or variants thereof, and a heterologous polypeptide sequence. Preferably, the VH and VL domains of the fusion protein correspond to the same scFv referred to in Table 1. In yet another embodiment, a fusion

protein of the invention comprises, or alternatively consists of a polypeptide having the amino acid sequence of any one, two, three or more of the VH CDRs referred to in Table 1 and the amino acid sequence of any one, two, three or more of the VL CDRs referred to in Table 1, or fragments or variants thereof, and a heterologous polypeptide sequence. Preferably, two, three, four, five, six, or more of the VHCDR(s) or VLCDR(s) correspond to the same scFv referred to in Table 1. Nucleic acid molecules encoding these fusion proteins are also encompassed by the invention.

[0243] The present invention also provides: antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that immunospecifically bind to the soluble form of BLyS; antibodies that immunospecifically bind to the membrane-bound form of BLyS; and antibodies that immunospecifically bind to both the soluble form and membrane-bound form of BLyS.

[0244] In one embodiment of the prescnt invention, antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to the soluble form of BLyS, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one or more of the VH domains contained in SEQ ID NOS:1563 – 1880 as disclosed in Table 1 and/or the amino acid sequence of any one or more of the VL domains contained in SEQ ID NOS: 1563 - 1880 as disclosed in Table 1, or fragment(s) or variant(s) (including derivative) thereof. Preferably, the VH and VL domains of the antibody correspond to the same scFv as disclosed in Table 1. In another embodiment, antibodies that immunospecifically bind to the soluble form of BLyS are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs contained SEQ ID NOS: 1563 - 1880 as disclosed in Table 1 and/or the amino acid sequence of any one, two, three, or more of the VL CDRs contained in SEQ ID NOS: 1563 - 1880 as diselosed in Table 1, or fragment(s) or variant(s) thereof. Preferably, two, three, four, five, six or more of the VH and VL CDRs of the antibody correspond to the same scFv as disclosed in Table 1. In a preferred embodiment, antibodies that immunospecifieally bind to the soluble form of BLyS are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one or more of the VH CDR3s contained in SEQ ID NOS: 1563 - 1880 as disclosed in Table 1 and/or the amino acid sequence of any one or more of the VL CDR3s contained in SEQ ID NOS:

1563 - 1880 as disclosed in Table 1, or fragment(s) or variant(s) thereof. Preferably, the VHCDR3 and VLCDR3 of the antibody correspond to the same scFv, as disclosed in Table 1. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0245] In another embodiment of the present invention, antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to the membrane-bound form of BLyS are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one or more of the VH domains contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1 and/or the amino acid sequence of any one or more of the VL domains contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1, or a fragment or variant thereof. Preferably, the VH and VL domains of the antibody correspond to the same seFv as disclosed in Table 1. In another embodiment, antibodies that immunospecifically bind to the membrane-bound form of BLyS are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1 and/or the amino acid sequence of any one, two, three, or more of the VL CDRs contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1, or fragment(s) or variant(s) thereof. Preferably, two, three, four, five, six or more of the VH and VL CDRs of the antibody correspond to the same scFv as disclosed in Table 1. In a preferred embodiment, antibodies that immunospecifically bind to the membrane-bound form of BLyS are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one or more of the VH CDR3s contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1 and/or the amino acid sequence of any one or more of the VL CDR3s contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1, or fragment(s) or variant(s) thereof. Preferably, the VHCDR3 and VLCDR3 of the antibody correspond to the same scFv, as disclosed in Table 1. Nucleic acid molecules eneoding these antibodies are also encompassed by the invention.

[0246] In another embodiment of the present invention, antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to the soluble form and membrane-bound form of BLyS, are provided that comprise, or alternatively consist of, a polypeptide having the

amino acid sequence of any one or more of the VH domains contained in SEQ ID NOS: 1 - 1562 as disclosed in Table 1 and/or the amino acid sequence of any one or more of the VL domains contained in SEQ ID NOS: 1 - 1562 as disclosed in Table 1, or a fragment or variant thereof. Preferably, the VH and VL domains of the antibody correspond to the same scFv as disclosed in Table 1. In another embodiment, antibodies that immunospecifically bind to the soluble form and membrane-bound form of BLyS are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs contained in SEQ ID NOS: 1 - 1562 as disclosed in Table 1 and/or the amino acid sequence of any one, two, three, or more of the VL CDRs contained in SEQ ID NOS: 1 - 1562 as disclosed in Table 1, or fragment(s) or variant(s) thereof. Preferably, two, three, four, five, six or more of the VH and VL CDRs of the antibody correspond to the same scFv as disclosed in Table 1. In a preferred embodiment, antibodies that immunospecifically bind to the soluble form and membrane-bound form of BLyS are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one or more of the VH CDR3s contained in SEQ ID NOS: 1 - 1562, disclosed in Table 1 and/or the amino acid sequence of any one or more of the VL CDR3s contained in SEQ ID NOS: 1 - 1562, disclosed in Table 1, or fragment(s) or variant(s) thereof. Preferably, the VHCDR3 and VLCDR3 of the antibody correspond to the same scFv, as disclosed in Table 1.

[0247] The present invention also provides for mixtures of antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to BLyS, wherein the mixture has at least one, two, three, four, five or more different antibodies of the invention. In particular, the invention provides for mixtures of different antibodies that immunospecifically bind to the soluble form of BLyS, the membrane-bound form of BLyS, and/or both the membrane-bound form and soluble form of BLyS. In specific embodiments, the invention provides mixtures of at least 2, preferably at least 4, at least 6, at least 8, at least 10, at least 12, at least 15, at least 20, or at least 25 different antibodies that immunospecifically bind to BLyS, wherein at least 1, at least 2, at least 4, at least 6, or at least 10, antibodies of the mixture is an antibody of the invention. In a specific embodiment, each antibody of the mixture is an antibody of the invention.

[0248] The present invention also provides for panels of antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to BLyS, wherein the panel has at least one, two, three, four, five or more different antibodies of the invention. In particular, the invention provides for panels of different antibodies that immunospecifically bind to the soluble form of BLyS, the membrane-bound form of BLyS, and/or both the membrane-bound form and soluble form of BLyS. In specific embodiments, the invention provides for panels of antibodies that have different affinities for BLyS, different specificities for BLyS, or different dissociation rates. The invention provides panels of at least 10, preferably at least 25, at least 50, at least 75, at least 100, at least 125, at least 150, at least 175, at least 200, at least 250, at least 300, at least 350, at least 400, at least 450, at least 500, at least 550, at least 600, at least 650, at least 700, at least 750, at least 800, at least 850, at least 900, at least 950, or at least 1000, antibodies. Panels of antibodies can be used, for example, in 96 well plates for assays such as ELISAs.

[0249] The present invention further provides for compositions comprising, one or more antibodies (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the invention). In one embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH domains contained in SEQ ID NOS:1563 - 1880 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR1s contained in SEQ ID NOS:1563 - 1880 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR2s contained in SEQ ID NOS:1563 - 1880 as disclosed in Table 1, or a variant thereof. In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR3s contained in SEQ ID NOS:1563 - 1880, as disclosed in Table 1 or a variant thereof.

[0250] The present invention further provides for compositions comprising, one or more antibodies (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the invention). In one embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH domains contained in SEQ ID NOS:1881 - 2128 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR1s contained in SEQ ID NOS:1881 - 2128 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR2s contained in SEQ ID NOS:1881 - 2128 as disclosed in Table 1, or a variant thereof. In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR3s contained in SEQ ID NOS:1881 - 2128 as disclosed in Table 1 or a variant thereof.

[0251] The present invention further provides for compositions comprising, one or more antibodies (including scFvs, or molecules comprising, or alternatively consisting of antibody fragments or variants of the invention). In one embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH domains contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR1s contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR2s contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1, or a variant thereof. In a preferred embodiment,

a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR3s contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1 or a variant thereof.

[0252] Other embodiments of the present invention providing for compositions comprising, one or more antibodies (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the invention) are listed below. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternative consist of, a polypeptide having an amino acid sequence of any one or more of the VL domains contained in SEQ ID NOS:1563 - 1880 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively eonsist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR1s contained in SEQ ID NOS:1563 - 1880 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR2s contained SEQ ID NOS:1563 - 1880 as disclosed in Table 1, or a variant thereof. In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR3s contained in SEQ ID NOS:1563 - 1880 as disclosed in Table 1, or a variant thereof.

[0253] Other embodiments of the present invention providing for compositions comprising, one or more antibodies (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the invention) are listed below. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino aeid sequence of any one or more of the VL domains contained in SEQ ID NOS:1881 - 2128 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide

having an amino acid sequenee of any one or more of the VL CDR1s contained in SEQ ID NOS:1881 - 2128 as diselosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR2s SEQ ID NOS:1881 - 2128 as disclosed in Table 1, or a variant thereof. In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR3s contained in SEQ ID NOS:1881 - 2128 as disclosed in Table 1, or a variant thereof.

[0254] Other embodiments of the present invention providing for compositions comprising, one or more antibodies (including scFvs and other moleeules comprising, or alternatively consisting of antibody fragments or variants of the invention) are listed below. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively eonsist of, a polypeptide having an amino acid sequence of any one or more of the VL domains contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR1s eontained in SEQ ID NOS:1 - 1562 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that eomprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR2s SEQ ID NOS:1 - 1562 as disclosed in Table 1, or a variant thereof. In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR3s contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1, or a variant thereof.

[0255] In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino aeid sequenee of any one or more of the VH domains in

disclosed in Table 1, or a variant thereof, and an amino acid sequence of any one or more of the VL domains disclosed in Table 1, or a variant thereof wherein the VH and VL domains are from scFvs with the same specificity (i.e., from scFvs that bind soluble BLyS (SEQ ID NOS:1563 - 1880), from scFvs that bind membrane-bound BLyS (SEQ ID 1881 - 2128), or from scFvs that bind both soluble and membrane-bound BLyS (SEQ ID NOS:1 – 1562). In a preferred embodiment the invention provides antibodies wherein the VH CDRX (where X=1,2, or 3) and VL CDRY (where Y= 1,2, or 3) are from scFvs with the same specificity (i.e., from scFvs that bind soluble BLyS (SEQ ID NOS:1563 - 1880), from scFvs that bind membrane-bound BLyS (SEQ ID NOS:1881 - 2128), or from scFvs that bind both soluble and membrane-bound BLyS (SEQ ID NOS:1 – 1562). In yet another embodiment, a composition of the present invention comprises one or more fusion proteins.

[0256] As discussed in more detail below, a composition of the invention may be used either alone or in combination with other compositions. The antibodies (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the present invention) may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically conjugated (including covalently and non-covalently conjugations) to polypeptides or other compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. See, *e.g.*, PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Patent No. 5,314,995; and EP 396,387.

[0257] Antibodies of the present invention (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the present invention) may be used, for example, but not limited to, to purify and detect BLyS, and to target the polypeptides of the present invention to cells expressing membrane-bound BLyS or BLyS receptor, including both *in vitro* and *in vivo* diagnostic and therapeutic methods. For example, the antibodies have use in immunoassays for qualitatively and quantitatively measuring levels of BLyS in biological samples. See, *e.g.*, Harlow *et al.*, Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988) (incorporated by reference herein in its entirety).

Methods Producing Antibodies

[0258] The antibodies of the invention (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the invention) can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by reeombinant expression techniques.

[0259] The single chain Fvs disclosed in Table 1 were generated using phage display methods known in the art. Furthermore, other scFvs that immunospecifically bind BLyS may be generated using phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage partieles which carry the polynucleotide sequences encoding them. In particular, DNA sequenees eneoding VH and VL domains are amplified from animal cDNA libraries (*e.g.*, human or murine cDNA libraries of lymphoid tissues) or synthetic eDNA libraries. The DNA encoding the VH and VL domains are joined together by an scFv linker by PCR and cloned into a phagemid vector (*e.g.*, p CANTAB 6 or pComb 3 HSS). The vector is electroporated in *E. coli* and the *E. coli* is infected with helper phage. Phage used in these methods are typically filamentous phage including fd and M13 and the VH and VL domains are usually recombinantly fused to either the phage gene III or gene VIII. Phage expressing an antigen binding domain that binds to an antigen of interest (*i.e.*, BLyS or a fragment thereof) can be selected or identified with antigen, *e.g.*, using labeled antigen or antigen bound or captured to a solid surface or bead. Examples of phage display methods that can be used to make the antibodies of the present invention include, but are not limited to, those disclosed in Brinkman *et al.*, J. Immunol. Methods 182:41-50 (1995); Ames *et al.*, J. Immunol. Methods 184:177-186 (1995); Kettleborough *et al.*, Eur. J. Immunol. 24:952-958 (1994); Persic *et al.*, Gene 187 9-18 (1997); Burton *et al.*, Advances in Immunology 57:191-280(1994); PCT application No. PCT/GB91/O1 134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/1 1236; WO 95/15982; WO 95/20401; WO97/13844; and U.S. Patent Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

[0260] ScFvs that immunospecifcally bind to both BLyS and APRIL polypeptides (preferably to the mature soluble forms of each) may be obtained, for example, by

sequential rounds of selection for binding to one or the other of BLyS and APRIL polypeptides. Thus in one embodiment, the present invention provides for a method of selecting phage that express scFvs that immunospecifically bind both BLyS polypeptides and APRIL polypeptides, comprising at least one round of phage selection for binding to BLyS polypeptide and at least one round of phage selection for binding to APRIL polypeptide. Selection for BLyS binding may either precede or follow selection for APRIL binding. More than one round of selection for binding to either BLyS or APRIL may be conducted.

[0261] ScFvs that immunospecifcally bind to a heterotrimer comprising at least one BLyS polypeptide and at least one APRIL polypeptide may be, for example, obtained by sequential rounds of selection for binding to one or the other of BLyS and APRIL polypeptide. Thus in one embodiment, the present invention provides for a method of selecting phage that express scFvs that immunospecifically bind a heterotrimer comprising at least one BLyS polypeptide and at least one APRIL polypeptide, comprising at least one round of phage selection for binding to BLyS polypeptide and at least one round of phage selection for binding to APRIL polypeptide. Selection for BLyS binding may either precede or follow selection for APRIL binding. More than one round of selection for binding to either BLyS or APRIL may be conducted.

[0262] Alternatively, scFvs that immunospecifcally bind to a heterotrimer comprising at least one BLyS polypeptide and at least one APRIL polypeptide may be obtained, for example, by selecting scFVs that bind to a BLyS heterotrimer. A BLyS heterotrimer may contain, for example, one BLyS polypeptide and two APRIL polypeptides (2BLyS:1APRIL heterotrimer). Other BLyS heterotrimers may contain, for example, one BLyS polypeptide and two APRIL polypeptides (1BLyS:2APRIL heterotrimer). Preferably, the heterotrimers comprising BLyS and APRIL polypeptides contain the mature forms of both the BLyS and APRIL polypeptides. ScFvs may be selected in one or more rounds of selection for binding only to the 2BLyS:1APRIL heterotrimer, or only to the 1BLyS:2APRIL heterotrimer. Alternatively, scFVs that immunospecifcally bind heterotrimers comprising BLyS and APRIL polypeptides may be obtained through sequential rounds of screening on individual forms of the BLyS/APRIL heterotrimer in any order and/or on both forms of the heterotrimer simultaneously, or any combination thereof.

[0263] As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, *e.g.*, as described below. Techniques to recombinantly produce Fab, Fab′ and F(ab′)2 fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92/22324; Mullinax *et al.*, BioTechniques 12(6):864-869 (1992); Sawai *et al.*, AJRI 34:26-34 (1995); and Better *et al.*, Science 240:1041-1043 (1988) (said references incorporated by reference in their entireties).

[0264] The charaeteristics of an antibody, such as its on-rate, off-rate and/or overall affinity may be altered using in vitro mutation and selection techniques. This process is well known in the art and is commonly referred to as in vitro affinity maturation of antibodies. Starting with a given antibody that binds a particular antigen with a certain affinity, one of skill in the art can engineer variants of that antibody and test the antibody variants for altered (usually improved) antigen binding characteristics. The amino acid sequence of the VH and VL regions of such antibody variants may be substantially from that of the starting or original antibody; for example, the an antibody variants may comprise the original VH or VL paired with a different (from the original) VL or VH region, respectively. Alternatively, the amino acid sequence of the VH and VL region of such antibody variants may be quite similar to that of the starting or original antibody; for example, an antibody variant may have only a few amino acid changes in the VH and/or VL region. It is common for one to engineer the mutations in CDR regions, and particularly in theVHCDR3 region. Examples of both types of in vitro antibody affinity maturation are described for example, Thompson et al., (1996) The Journal of Molecular Biology 256:77-88. Moreover, a review of phage display antibody technology may be found in Vaughan et al., (1998) Nature Biotechnology 16:535-539; both of these articles are herein incorporated by reference in their entireties. The scFvs of SEQ ID NOS:10-37 are CDR3 mutants derived from the scFv of SEQ ID NO:9 and scFvs of SEQ ID NOS:291-327 are CDR3 mutants derived from the scFv of SEQ ID NO:2.

[0265] To generate whole antibodies, PCR primers including VH or VL nucleotide sequences, a restriction site, and a flanking sequence to protect the restriction site can be used to amplify the VH or VL sequences in scFv clones. Utilizing cloning techniques

known to those of skill in the art, the PCR amplified VH domains can be cloned into vectors expressing a VH constant region, *e.g.*, the human gamma 4 constant region, and the PCR amplified VL domains can be cloned into vectors expressing a VL constant region, *e.g.*, human kappa or lambda constant regions. Preferably, the vectors for expressing the VH or VL domains comprise a promoter suitable to direct expression of the heavy and light chains in the chosen expression system, a secretion signal, a cloning site for the immunoglobulin variable domain, immunoglobulin constant domains, and a selection marker such as neomycin. The VH and VL domains may also be cloned into one vector expressing the necessary constant regions. The heavy chain conversion vectors and light chain conversion vectors are then co-transfected into cell lines to generate stable or transient cell lines that express full-length antibodies, *e.g.*, IgG, using techniques known to those of skill in the art.

[0266] Cell lines that express antibodies that comprise the VH and VL domains of scFvs of the invention have been deposited with the American Type Culture Collection ("ATCC") on the dates listed in Table 2 and given the ATCC Deposit Numbers identified in Table 2. The ATCC is located at 10801 University Boulevard, Manassas, VA 20110-2209, USA. The ATCC deposit was made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for purposes of patent procedure.

Table 2

Cell Line	Corresponding scFv	SEQ ID NO:	ATCC Deposit Number	ATCC Deposit Date
NSO-B11-15	I050B11-15	24	PTA-3238	March 27, 2001
NSO-anti-BLyS-6D08-18	I006D08	2	PTA-3239	March 27, 2001
NSO- anti-BLyS-116A01-60	I116A01	327	PTA-3240	March 27, 2001
IO26C04K	I026C04-K	1563	PTA-3241	March 27, 2001
IO50A12	I050A12	12	PTA-3242	March 27, 2001
IO50-B11	I050B11	9	PTA-3243	March 27, 2001

[0267] Accordingly, in one embodiment, the invention provides antibodies that comprise the VH and VL domains of scFvs of the invention.

[0268] In a preferred embodiment, an antibody of the invention is the antibody expressed by cell line NSO-B11-15.

[0269] In a preferred embodiment, an antibody of the invention is the antibody expressed by cell line NSO-anti-BLyS-6D08-18.

[0270] In a preferred embodiment, an antibody of the invention is the antibody expressed by cell line NSO- anti-BLyS-116A01-60.

[0271] In a preferred embodiment, an antibody of the invention is the antibody expressed by cell line IO26C04K.

[0272] In a preferred embodiment, an antibody of the invention is the antibody expressed by cell line IO50A12.

[0273] In a preferred embodiment, an antibody of the invention is the antibody expressed by cell line NSO-B11.

[0274] In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a BLyS polypeptide. In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a BLyS polypeptide by between 1% and 10% in a competitive inhibition assay. In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a BLyS polypeptide by between 1% and 10% in a competitive inhibition assay.

[0275] In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a BLyS polypeptide by at least 10% and up to 20% in a competitive inhibition assay.

[0276] In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv

referred to in Table 1 to a BLyS polypeptide by at least 20% and up to 30% in a competitive inhibition assay.

[0277] In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a BLyS polypeptide by at least 30% and up to 40% in a competitive inhibition assay.

[0278] In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a BLyS polypeptide by at least 40% and up to 50% in a competitive inhibition assay.

[0279] In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a BLyS polypeptide by at least 50% and up to 60% in a competitive inhibition assay.

[0280] In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a BLyS polypeptide by at least 60% and up to 70% in a competitive inhibition assay.

[0281] In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a BLyS polypeptide by at least 70% and up to 80% in a competitive inhibition assay.

[0282] In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a BLyS polypeptide by at least 80% and up to 90% in a competitive inhibition assay.

[0283] In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a BLyS polypeptide by at least 90% and up to 100% in a eompetitive inhibition assay.

[0284] In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of the antibody produced by the cell line having ATCC deposit number PTA-3238 to a BLyS polypeptide.

[0285] In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of the antibody produced by the cell line having ATCC deposit number PTA-3239 to a BLyS polypeptide.

[0286] In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of the antibody produced by the cell line having ATCC deposit number PTA-3240 to a BLyS polypeptide.

[0287] In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of the antibody produced by the cell line having ATCC deposit number PTA-3241 to a BLyS polypeptide.

[0288] In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of the antibody produced by the cell line having ATCC deposit number PTA-3242 to a BLyS polypeptide.

[0289] In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of the antibody produced by the cell line having ATCC deposit number PTA-3243 to a BLyS polypeptide.

[0290] For some uses, including *in vivo* use of antibodies in humans and *in vitro* detection assays, it may be preferable to use human or chimeric antibodies. Completely human antibodies are particularly desirable for therapeutic treatment of human patients. See also, U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO98/16654, WO 96/34096, WO 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety. In a specific embodiment, antibodies of the present invention comprise one or more VH and VL domains corresponding to the human scFvs of the invention and framework regions from another immunoglobulin molecule, preferably a human immunoglobulin molecule. In a

specific embodiment, antibodies of the present invention comprise one or more CDRs corresponding to the human scFvs of the invention and framework regions from another immunoglobulin molecule, preferably a human immunoglobulin molecule. In other embodiments, an antibody of the present invention eomprises one, two, three, four, five, six or more VL CDRs or VH CDRs corresponding to one or more of the human scFvs referred to in Table 1, or fragments or variants thereof, and framework regions (and, optionally CDRs not derived from the scFvs in Table 1) from a human immunoglobulin molecule. In a preferred embodiment, an antibody of the present invention comprises a VH CDR3, VL CDR3, or both, corresponding to the same seFv, or different scFvs referred to in Table 1, or fragments or variants thereof, and framework regions from a human immunoglobulin.

[0291] A chimeric antibody is a molecule in which different portions of the antibody are derived from different immunoglobulin molecules such as antibodies having a variable region derived from a human antibody and a non-human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. See *e.g.*, Morrison, Science 229:1202 (1985); Oi *et al.*, BioTechniques 4:214 (1986); Gillies *et al.*, J. Immunol. Methods 125:191-202 (1989); U.S. Patent Nos. 5,807,715; 4,816,567; and 4,816,397, which are incorporated herein by reference in their entirety. Chimerie antibodies comprising one or more CDRs from human species and framework regions from a non-human immunoglobulin molecule (*e.g.*, framework regions from a canine or feline immunoglobulin molecule) can be produced using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Patent Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, Molecular Immunology 28(4/5):489-498 (1991); Studnicka *et al.*, Protein Engineering 7(6):805-814 (1994); Roguska *et al.*, PNAS 91:969-973 (1994)), and chain shuffling (U.S. Patent No. 5,565,332). In a preferred embodiment, chimeric antibodies comprise a human CDR3 having an amino acid sequence of any one of the VH CDR3s or VL CDR3s referred to in Table 1, or a variant thereof, and non-human framework regions or human framework regions different from those of the frameworks in the corresponding scFv disclosed in Table 1. Often, framework residues in the framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These

framework substitutions are identified by methods well known in the art, *e.g.*, by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, *e.g.*, Queen *et al.*, U.S. Patent No. 5,585,089; Riechmann *et al.*, Nature 332:323 (1988), which are incorporated herein by reference in their entireties.)

[0292] Further, the antibodies of the invention can, in turn, be utilized to generate anti-idiotype antibodies that "mimic" BLyS polypeptides using techniques well known to those skilled in the art. (See, *e.g.*, Greenspan & Bona, FASEB J. 7(5):437-444 (1993); and Nissinoff, J. Immunol. 147(8):2429-2438 (1991)). For example, antibodies of the invention which bind to BLyS and competitively inhibit the binding of BLyS to its receptor (as determined by assays well known in the art such as, for example, that disclosed, *infra*) can be used to generate antiidiotypes that "mimic" a BLyS ligand/receptor-binding domain and, as a consequence, bind to and neutralize BLyS receptors (e.g., TACI - GenBank accession number AAC51790; BCMA - GenBank accession number NP_001183; and/or BAFF-R - GenBank accession number NP_443177). Such neutralizing anti-idiotypes (including molecules comprising, or alternatively consisting of, antibody fragments or variants, such as Fab fragments of such anti-idiotypes) can be used in therapeutic regimens to neutralize BLyS. For example, such anti-idiotypic antibodies can be used to bind BLyS ligands/receptors, and thereby block BLyS mediated biological activity. Alternatively, anti-idiotypes that "mimic" a BLyS binding domain may bind to BLyS receptor(s) and induce BLyS receptor mediated signalling (e.g., activation of nuclear factor of activated T cells (NF-AT), nuclear factor-kappa B (NF-kappa B), and/or AP-1). Such agonistic anti-idiotypes (including agonistic Fab fragments of these anti-idiotypes) can be used in therapeutic regimens to induce or enhance BLyS receptor mediated signalling. For example, such anti-idiotypic antibodies can be used to bind BLyS ligands/receptors, and thereby stimulate BLyS mediated biological activity (e.g., B cell proliferation and/or immunoglobulin production).

[0293] Once an antibody molecule of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) has been chemically synthesized or recombinantly expressed, it may be purified by any method known in the art for purification of an immunoglobulin molecule, or more generally, a protein molecule,

such as, for example, by chromatography (*e.g.*, ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. Further, the antibodies of the present invention may be fused to heterologous polypeptide sequences described herein or otherwise known in the art, to facilitate purification.

Polynucleotides Encoding an Antibody

[0294] The invention provides polynucleotides comprising, or alternatively consisting of, a nucleotide sequence encoding an antibody of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof). The invention also encompasses polynucleotides that hybridize under high stringency, or alternatively, under intermediate or lower stringency hybridization conditions, *e.g.*, as defined *supra*, to polynucleotides complementary to nucleic acids having a polynucleotide sequence that encodes an antibody of the invention or a fragment or variant thereof.

[0295] The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. Since the amino acid sequences of the scFv antibodies and VH domains, VL domains and CDRs thereof, are known (as described in Table 1), nucleotide sequences encoding these antibodies can be determined using methods well known in the art, *i.e.*, the nucleotide codons known to encode the particular amino acids are assembled in such a way to generate a nucleic acid that encodes the antibody, of the invention. Such a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides (*e.g.*, as described in Kutmeier *et al.*, BioTechniques 17:242 (1994)), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

[0296] Alternatively, a polynucleotide encoding an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or

obtained from a suitable source (*e.g.*, an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A+ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma eells selected to express an antibody of the invention) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, *e.g.*, a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

[0297] Once the nucleotide sequence of the antibody (ineluding molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, *e.g.*, recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques deseribed in Sambrook *et al.*, 1990, Molecular Cloning, A Laboratory Manual, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY and Ausubel *et al.*, eds., 1998, Current Protoeols in Molecular Biology, John Wiley & Sons, NY, which are both incorporated by reference herein in their entireties), to generate antibodies having a different amino aeid sequence, for example to ereate amino acid substitutions, deletions, and/or insertions.

[0298] In a specific embodiment, one or more of the VH and VL domains referred to in Table 1, or fragments or variants thereof, is inserted within framework regions using reeombinant DNA techniques known in the art. In a specific embodiment, one, two, three, four, five, six, or more of the CDRs referred to in Table 1, or fragments or variants thereof, is inserted within framework regions using recombinant DNA techniques known in the art. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, *e.g.*, Chothia *et al.*, J. Mol. Biol. 278: 457-479 (1998) for a listing of human framework regions, the contents of which are hereby incorporated by reference in its entirety). Preferably, the polynucleotides generated by the combination of the framework regions and CDRs encode an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that specifically binds to BLyS. Preferably, as discussed *supra*, polynucleotides encoding variants of antibodies or antibody fragments having one or more amino acid substitutions may be made within the framework regions, and, preferably, the

amino acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules, or antibody fragments or variants, lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and fall within the ordinary skill of the art.

Recombinant Expression of an Antibody

[0299] Recombinant expression of an antibody of the invention (including seFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof (*e.g.*, a heavy or light chain of an antibody of the invention or a portion thereof or a single chain antibody of the invention)), requires construction of an expression veetor(s) containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule (e.g., a whole antibody, a heavy or light chain of an antibody, or portion thereof (preferably, but not necessarily, containing the heavy or light chain variable domain)), of the invention has been obtained, the vector(s) for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. The invention, thus, provides replicable vectors comprising a nueleotide sequence encoding an antibody molecule of the invention (e.g., a whole antibody, a heavy or light chain of an antibody, a heavy or light chain variable domain of an antibody, or a portion thereof, or a heavy or light chain CDR, a single chain Fv, or fragments or variants thereof), operably linked to a promoter. Such vectors may include the nueleotide sequence eneoding the eonstant region of the antibody molecule (see, e.g., PCT Publication WO 86/05807; PCT Publication WO 89/01036; and U.S. Patent No. 5,122,464, the contents of each of whieh are hereby incorporated by reference in its entirety) and the variable domain of the antibody may be cloned into such a vector for

expression of the entire heavy chain, the entire light chain, or both the entire heavy and light chains.

[0300] The expression vector(s) is(are) transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody of the invention. Thus, the invention ineludes host cells containing polynucleotide(s) encoding an antibody of the invention (e.g., whole antibody, a heavy or light chain thereof, or portion thereof, or a single chain antibody of the invention, or a fragment or variant thereof), operably linked to a heterologous promoter. In preferred embodiments, for the expression of entire antibody molecules, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

[0301] A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention *in situ*. These include, but are not limited to, microorganisms such as bacteria (*e.g.*, *E. coli, B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (*e.g.*, *Saccharomyces, Pichia*) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (*e.g.*, baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (*e.g.*, Ti plasmid) containing antibody coding sequences; or mammalian cell systems (*e.g.*, COS, CHO, BHK, 293, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (*e.g.*, metallothionein promoter) or from mammalian viruses (*e.g.*, the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as *Escherichia coli*, and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector

such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking *et al.*, Gene 45:101 (1986); Cockett *et al.*, Bio/Technology 8:2 (1990)).

[0302] In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited to, the *E. coli* expression vector pUR278 (Ruther *et al.*, EMBO 1. 2:1791 (1983)), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, Nucleic Acids Res. 13:3101-3109 (1985); Van Heeke & Schuster, J. Biol. Chem. 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione 5-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

[0303] In an insect system, Autographa californica nuclear polyhedrosis virus (AcNPV) may be used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. Antibody coding sequences may be cloned individually into non-essential regions (for example, the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example, the polyhedrin promoter).

[0304] In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, *e.g.*, the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by *in vitro* or *in vivo* recombination. Insertion in a non-essential region of the viral genome (*e.g.*, region El or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts (*e.g.*, see Logan & Shenk, Proc. Natl. Acad. Sci. USA 8 1:355-359 (1984)).

Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation eodon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation eodons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see, *e.g.*, Bittner *et al.*, Methods in Enzymol. 153:51-544 (1987)).

[0305] In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (*e.g.*, glycosylation) and processing (*e.g.*, cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper proeessing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include, but are not limited to, CHO, VERY, BHK, Hela, COS, NSO, MDCK, 293, 3T3, W138, and in particular, breast cancer cell lines such as, for example, BT483, Hs578T, HTB2, BT2O and T47D, and normal mammary gland cell line such as, for example, CRL7O3O and HsS78Bst.

[0306] For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (*e.g.*, promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which

express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compositions that interact directly or indirectly with the antibody molecule.

[0307] A number of selection systems may be used, including but not limited to, the herpes simplex virus thymidine kinase (Wigler *et al.*, Cell 11:223 (1977)), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, Proc. Natl. Acad. Sci. USA 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy *et al.*, Cell 22:8 17 (1980)) genes can be employed in tk-, hgprt- or aprt- cells, respectively. Also, antimetabolite resistance can be used as the basis of seleetion for the following genes: *dhfr*, which confers resistance to methotrexate (Wigler *et al.*, Natl. Acad. Sci. USA 77:357 (1980); O'Hare *et al.*, Proc. Natl. Acad. Sci. USA 78:1527 (1981)); *gpt*, which confers resistance to mycophenolic acid (Mulligan & Berg, Proc. Natl. Acad. Sci. USA 78:2072 (1981)); neo, which confers resistance to the aminoglycoside G-418 (Clinical Pharmacy 12:488-505; Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Bioehem. 62: 191-217 (1993); TIB TECH 11(5):155-2 15 (May, 1993)); and *hygro*, which eonfers resistance to hygromycin (Santerre *et al.*, Gene 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to seleet the desired recombinant elone, and such methods are described, for example, in Ausubel *et al.* (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli *et al.* (eds), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colberre-Garapin *et al.*, J. Mol. Biol. 150:1 (1981), which are incorporated by referenee herein in their entireties.

[0308] The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol.3. (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, inerease in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the coding sequence of the antibody, production of the antibody will also increase (Crouse *et al.*, Mol. Cell. Biol. 3:257 (1983)).

[0309] The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain is preferably placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, Nature 322:52 (1986); Kohler, Proc. Natl. Acad. Sci. USA 77:2 197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

[0310] Once an antibody molecule of the invention has been produced by recombinant expression, it may be purified by any method known in the art for purification of an immunoglobulin molecule, or more generally, for purification of a protein, for example, by chromatography (*e.g.*, ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. Further, the antibodies of the present invention may be fused to heterologous polypeptide sequences described herein or otherwise known in the art to facilitate purification.

[0311] Antibodies of the present invention include naturally purified products, products of chemical synthetic procedures, and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect and mammalian cells. Depending upon the host employed in a recombinant production procedure, the antibodies of the present invention may be glycosylated or may be non-glycosylated. In addition, antibodies of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes.

[0312] Antibodies of the invention can be chemically synthesized using techniques known in the art (e.g., see Creighton, 1983, Proteins: Structures and Molecular Principles, W.H. Freeman & Co., N.Y., and Hunkapiller, M., et al., 1984, Nature 310:105-111). For example, a peptide corresponding to a fragment of an antibody of the invention can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the antibody polypeptide sequence. Non-classical amino acids include, but are not limited

to, to the D-isomers of the common amino acids, 2,4-diaminobutyric acid, a-amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, g-Abu, e-Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyrie acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyelohexylalanine, b-alanine, fluoro-amino acids, designer amino acids such as b-methyl amino acids, Ca-methyl amino acids, Na-methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

[0313] The invention eneompasses antibodies which are differentially modified during or after translation, e.g., by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/bloeking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, ehymotrypsin, papain, V8 protease, $NaBH_4$, acetylation, formylation, oxidation, reduction, metabolie synthesis in the presence of tunicamycin, etc.

[0314] Additional post-translational modifieations encompassed by the invention include, for example, e.g., N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends), attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of procaryotic host cell expression. The polypeptides may also be modified with a detectable label, such as an enzymatic, fluorescent, radioisotopic or affinity label to allow for detection and isolation of the antibody.

[0315] Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, glucose oxidase or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include biotin, umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include a radioactive metal ion, e.g., alpha-emitters such as,

for example, ^{213}Bi, or other radioisotopes such as, for example, iodine (^{131}I, ^{125}I, ^{123}I, ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{115m}In, ^{113m}In, ^{112}In, ^{111}In), and technetium (^{99}Tc, ^{99m}Tc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re, ^{188}Re, ^{142}Pr, ^{105}Rh, ^{97}Ru, ^{68}Ge, ^{57}Co, ^{65}Zn, ^{85}Sr, ^{32}P, ^{153}Gd, ^{169}Yb, ^{51}Cr, ^{54}Mn, ^{75}Se, ^{113}Sn, and ^{117}Tin.

[0316] In specific embodiments, antibodies of the invention may be labeled with Europium. For example, antibodies of the invention may be labelled with Europium using the DELFIA Eu-labeling kit (catalog# 1244-302, Perkin Elmer Life Sciences, Boston, MA) following manufacturer's instructions.

[0317] In specific embodiments, antibodies of the invention are attached to macrocyclic chelators useful for conjugating radiometal ions, including but not limited to, ^{111}In, ^{177}Lu, ^{90}Y, ^{166}Ho, and ^{153}Sm, to antibodies. In a preferred embodiment, the radiometal ion associated with the macrocyclic chelators attached to antibodies of the invention is ^{111}In. In another preferred embodiment, the radiometal ion associated with the macrocyclic chelator attached to antibodies of the invention is ^{90}Y. In specific embodiments, the macrocyclic chelator is 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA). In specific embodiments, the macrocyclic chelator is α-(5-isothiocyanato-2-methoxyphenyl)-1,4,7,10-tetraaza- cyclododecane-1,4,7,10-tetraacetic acid. In other specific embodiments, the DOTA is attached to the antiboddy of the invention via a linker molecule. Examples of linker molecules useful for conjugating DOTA to an antibody are commonly known in the art - see, for example, DeNardo et al., Clin Cancer Res. 4(10):2483-90, 1998; Peterson et al., Bioconjug. Chem. 10(4):553-7, 1999; and Zimmerman et al, Nucl. Med. Biol. 26(8):943-50, 1999 which are hereby incorporated by reference in their entirety. In addition, U.S. Patents 5,652,361 and 5,756,065, which disclose chelating agents that may be conjugated to antibodies, and methods for making and using them, are hereby incorporated by reference in their entireties.

[0318] In one embodiment, antibodies of the invention are labeled with biotin. In other related embodiments, biotinylated antibodies of the invention may be used, for example, as an imaging agent or as a means of identifying one or more BLyS receptor(s) or other coreceptor or ligand molecules.

[0319] Also provided by the invention are chemically modified derivatives of antibodies of the invention which may provide additional advantages such as increased solubility, stability and in vivo or in vitro cireulating time of the polypeptide, or decreased immunogenicity (see U. S. Patent No. 4,179,337). The chemical moieties for derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, earboxymethylcellulose, dextran, polyvinyl alcohol and the like. The polypeptides may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attaehed ehemical moieties.

[0320] The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred moleeular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degrec or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 25,000, 30,000, 35,000, 40,000, 50,000, 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, or 100,000 kDa.

[0321] As noted above, the polyethylene glycol may have a branched structure. Branched polyethylene glycols are described, for example, in U.S. Patent No. 5,643,575; Morpurgo *et al., Appl. Biochem. Biotechnol. 56*:59-72 (1996); Vorobjev *et al., Nucleosides Nucleotides 18*:2745-2750 (1999); and Caliceti *et al., Bioconjug. Chem. 10*:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

[0322] The polyethylene glycol molecules (or other chemical moieties) should be attached to the protein with consideration of effects on functional or antigenic domains of the antibody. There are a number of attachment methods available to those skilled in the art, e.g., EP 0 401 384, herein incorporated by reference (coupling PEG to G-CSF), see

also Malik et al., Exp. Hematol. 20:1028-1035 (1992) (reporting pegylation of GM-CSF using tresyl chloride). For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as, a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glyeol molecule may be bound. The amino acid residues having a free amino group may include, for example, lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues, glutamic acid residues, and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

[0323] As suggested above, polyethylene glycol may be attached to proteins, e.g., antibodies, via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to a proteins via covalent bonds to lysine, histidine, aspartic acid, glutamic aeid, or cysteine residues. One or more reaction chemistries may be employed to attaeh polyethylene glycol to specific amino acid residues (e.g., lysine, histidine, aspartic acid, glutamic acid, or cysteine) of the antibody or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, eysteine and combinations thereof) of the antibody.

[0324] One may specifically desire antibodies chemically modified at the N-terminus of either the heavy chain or the light chain or both. Using polyethylene glycol as an illustration, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein (or peptide) molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated preparation (i.e., separating this moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated protein molecules. Selective chemical modification at the N-terminus may be accomplished by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular antibody, e.g., a heavy chain or alight chain. Under the appropriate reaction conditions, substantially selective

derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

[0325] As indicated above, pegylation of the proteins of the invention may be accomplished by any number of means. For example, polyethylene glycol may be attached to the protein either directly or by an intervening linker. Linkerless systems for attaching polyethylene glycol to proteins are described in Delgado *et al., Crit. Rev. Thera. Drug Carrier Sys. 9*:249-304 (1992); Francis *et al., Intern. J. of Hematol. 68*:1-18 (1998); U.S. Patent No. 4,002,531; U.S. Patent No. 5,349,052; WO 95/06058; and WO 98/32466, the disclosures of each of whieh are incorporated herein by reference.

[0326] One system for attaching polyethylene glyeol directly to amino acid residues of proteins without an intervening linker employs tresylated MPEG, which is produced by the modification of monmethoxy polyethylene glycol (MPEG) using tresylchloride ($ClSO_2CH_2CF_3$). Upon reaction of antibody with tresylated MPEG, polyethylene glycol is directly attached to amine groups of the antibody. Thus, the invention includes antibody-polyethylene glycol conjugates produced by reacting proteins of the invention with a polyethylene glycol molecule having a 2,2,2-trifluoreothane sulphonyl group.

[0327] Polyethylene glycol can also be attached to antibodies using a number of different intervening linkers. For example, U.S. Patent No. 5,612,460, the entire disclosure of which is incorporated herein by reference, discloses urethane linkers for connecting polyethylene glycol to proteins. Protein-polyethylene glycol conjugates wherein the polyethylene glycol is attached to the antibody by a linker can also be produeed by reaction of antibodies with compounds such as MPEG-succinimidylsuccinate, MPEG activated with 1,1'-carbonyldiimidazole, MPEG-2,4,5-trichloropenylcarbonate, MPEG-p-nitrophenolcarbonate, and various MPEG-succinate derivatives. A number additional polyethylene glycol derivatives and reaction ehemistries for attaching polyethylene glycol to proteins are described in WO 98/32466, the entire disclosure of which is incorporated herein by reference. Pegylated protein products produced using the reaction chemistries set out herein are included within the scope of the invention.

[0328] The number of polyethylene glycol moieties attached to each antibody of the invention (*i.e.*, the degree of substitution) may also vary. For example, the pegylated antibodies of the invention may be linked, on average, to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15,

17, 20, or more polyethylene glycol molecules. Similarly, the average degree of substitution within ranges such as 1-3, 2-4, 3-5, 4-6, 5-7, 6-8, 7-9, 8-10, 9-11, 10-12, 11-13, 12-14, 13-15, 14-16, 15-17, 16-18, 17-19, or 18-20 polyethylene glycol moieties per antibody molecule. Methods for determining the degree of substitution are discussed, for example, in Delgado *et al., Crit. Rev. Thera. Drug Carrier Sys. 9*:249-304 (1992).

Antibody Characterization

[0329] Antibodies of the present invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be characterized in a variety of ways. In particular, antibodies and related molecules of the invention may be assayed for the ability to immunospeeifically bind to BLyS or a fragment of BLyS (e.g., to the soluble form or the membrane-bound form of BLyS) using techniques described herein or routinely modifying techniques known in the art. BLyS or BLyS fragments that may be immunospecifically bound by the compositions of the invention include, but are not limited to, human BLyS (SEQ ID NOS:3228 and/or 3229) or BLyS expressed on human monocytes; murine BLyS (SEQ ID NOS:3230 and/or 3231) or BLyS expressed on murine monocytes; rat BLyS (either the soluble forms as given in SEQ ID NOS:3232, 3233, 3234 and/or 3235 or in a membrane associated form, *e.g.*, on the surface of rat monocytes); or monkey BLyS (e.g., the monkey BLyS polypeptides of SEQ ID NOS:3236 and/or 3237, the soluble form of monkey BLyS, or BLyS expressed on monkey monocytes) or fragments thereof. Preferably compositions of the invention bind human BLyS (SEQ ID NOS:3228 and/or 3229) or fragments thereof. Assays for the ability of the antibodies of the invention to immunospecifically bind BLyS or a fragment of BLyS may be performed in solution (*e.g.*, Houghten, Bio/Techniques 13:412-421(1992)), on beads (*e.g.*, Lam, Nature 354:82-84 (1991)), on chips (*e.g.*, Fodor, Nature 364:555-556 (1993)), on bacteria (*e.g.*, U.S. Patent No. 5,223,409), on spores (*e.g.*, Patent Nos. 5,571,698; 5,403,484; and 5,223,409), on plasmids (*e.g.*, Cull et al., Proc. Natl. Acad. Sci. USA 89:1865-1869 (1992)) or on phage (*e.g.*, Scott and Smith, Science 249:386-390 (1990); Devlin, Science 249:404-406 (1990); Cwirla et al., Proc. Natl. Acad. Sci. USA 87:6378-6382 (1990); and Felici, J. Mol. Biol. 222:301-310 (1991)) (each of these references is incorporated herein in its entirety by reference). Antibodies that have been identified to immunospecifically bind to BLyS or a fragment of BLyS can then be

assayed for their specificity and affinity for BLyS or a fragment of BLyS using or routinely modifying techniques described herein or otherwise known in the art.

[0330] The antibodies of the invention may be assayed for immunospecific binding to BLyS and cross-reactivity with other antigens by any method known in the art. In particular, the ability of an antibody to immunospecifically bind to the soluble form or membrane-bound form of BLyS and the specificity of the antibody, fragment, or variant for BLyS polypeptide from a particular species (e.g., murine, monkey or human, preferably human) may be determined using or routinely modifying techniques described herein or otherwise known in art .

[0331] Immunoassays whieh ean be used to analyze immunospecific binding and cross-reactivity include, but are not limited to, competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, and protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Ine., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

[0332] Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X-100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (*e.g.*, EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (*e.g.*, 1 to 4 hours) at 40 degrees C, adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 40 degrees C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a particular antigen can be assessed by, *e.g.*, western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (*e.g.*, pre-clearing the cell lysate with sepharose beads). For

further discussion regarding immunoprecipitation protocols see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.16.1.

[0333] Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (*e.g.*, 8%- 20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (*e.g.*, PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (*e.g.*, PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, *e.g.*, an anti-human antibody) conjugated to an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase) or radioactive molecule (*e.g.*, ^{32}P or ^{125}I) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.8.1.

[0334] ELISAs comprise preparing antigen, coating the well of a 96-well microtiter plate with the antigen, washing away antigen that did not bind the wells, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase) to the wells and incubating for a period of time, washing away unbound antibodies or non-specifically bound antibodies, and detecting the presence of the antibodies specifically bound to the antigen coating the well. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, the detectable molecule could be the antigen conjugated to a detectable compound such as an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase). One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the

signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 11.2.1.

[0335] The binding affinity of an antibody (including an scFv or other molecule comprising, or alternatively consisting of, antibody fragments or variants thereof) to an antigen and the off-rate of an antibody-antigen interaction can be determined by eompetitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (*e.g.*, ^{3}H or ^{125}I) with the antibody of interest in the presenee of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of the present invention for BLyS and the binding off-rates ean be determined from the data by Scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, BLyS is incubated with an antibody of the present invention conjugated to a labeled eompound (*e.g.*, ^{3}H or ^{125}I) in the presence of increasing amounts of an unlabeled seeond anti-BLyS antibody.

[0336] In a preferred embodiment, BIAcore kinetic analysis is used to determine the binding on and off rates of antibodies (including an scFv or other molecule comprising, or alternatively consisting of, antibody fragments or variants thereof) to BLyS, or fragments of BLyS. BIAeore kinetic analysis comprises analyzing the binding and dissociation of BLyS from chips with immobilized antibodies on their surface as described in detail in Examples 6, 12, 17 and 18, *infra.*

[0337] The antibodies of the invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) can also be assayed for their ability to inhibit, increase, or not significantly alter, the binding of BLyS to a BLyS receptor (e.g., TACI - GenBank accession number AAC51790; BCMA - GenBank accession number NP_001183; and/or BAFF-R - GenBank accession number NP_443177) using techniques known to those of skill in the art. For example, cells expressing a receptor for BLyS (e.g., IM9, REH, ARH-77cells, Namalwa, and RPMI-8226 B cell tumor lines as wells as peripheral CD20+ B cells) can be contacted with BLyS in the presence or absence of an antibody, and the ability of the antibody to inhibit, increase, or not significantly alter, BLyS binding to the cells can be measured. BLyS binding to cells can be measured by, for example, flow cytometry or a scintillation assay. BLyS or

the antibody can be labeled with a detectable compound such as a radioactive label (*e.g.*, ^{32}P, ^{35}S, and ^{125}I) or a fluorescent label (*e.g.*, fluorescein isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin, o-phthaldehyde and fluorescamine) to enable detection of an interaetion between BLyS and a BLyS receptor and/or BLyS and an antibody of the invention. Alternatively, the ability of antibodies of the invention to inhibit, increase, or not significantly alter, BLyS binding to a BLyS receptor can be determined in cell-free assays. For example, native or recombinant BLyS (e.g., that having the amino acid sequence of amino acids 134 – 285 of SEQ ID NO:3228) or a fragment thereof can be contacted with an antibody and the ability of the antibody to inhibit, increase, or not significantly alter, BLyS from binding to a BLyS receptor can be determined. Preferably, the antibody is immobilized on a solid support and BLyS or a BLyS fragment is labeled with a detectable compound. Alternatively, BLyS or a BLyS fragment is immobilized on a solid support and the antibody is labeled with a detectable compound. BLyS may be partially or completely purified (*e.g.*, partially or completely free of other polypeptides) or part of a cell lysate. Further, the BLyS polypeptide may be a fusion protein comprising BLyS or a biologically active portion thereof and a domain such as an Immunoglobulin Fc or glutathionine-S-transferase. For example, amino acid residues 1-154 of TACI (GenBank accession number AAC51790), or 1-48 of BCMA (GenBank accession number NP_001183) may be fused to the Fc region of an IgG molecule and used in a cell free assay to determine the ability of antibodies of the invention to inhibit, increase, or not significantly alter, BLyS binding to a BLyS receptor. Alternatively, BLyS can be biotinylated using techniques well known to those of skill in the art (*e.g.*, biotinylation kit, Pierce Chemicals; Rockford, IL).

[0338] The antibodies of the invention (including scFvs or other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), can also be assayed for their ability to inhibit, stimulate, or not significantly alter, BLyS-induced B-cell proliferation using techniques known to those of skill in the art. For example, B-cell proliferation can be assayed by ^{3}H-thymidine incorporation assays and trypan blue cell counts (see, *e.g.*, Moore *et al.*, Science 285: 260-263 (1999)). Further, the antibodies of the invention, or fragments or variants thereof, can be assayed for their ability to block, stimulate, or not significantly alter, BLyS-induced activation of cellular signaling molecules and transcription factors such as calcium-modulator and cyclophilin ligand

("CAML"), calcineurin, nuclear factor of activated T cells transcription faetor ("NF-AT"), nuclear factor-kappa B ("NF-kappa B"), and AP-1 using techniques known to those of skill in the art (see, *e.g.*, von Bulow and Bram, Science 278:138-141(1997)). For example, NF-AT activity can be determined by electromobility gel shift assays, by detecting the expression of a protein known to be regulated by NF-AT (*e.g.*, IL-2 expression), by detecting the induetion of a reporter gene (*e.g.*, an NF-AT regulatory element operably linked to a nucleic acid encoding a detectable marker such as luciferase, beta-galaetosidase or chloramphenicol acetyltransferase (CAT)), or by detecting a cellular response (*e.g.*, cellular differentiation, or cell proliferation).

[0339] The antibodies of the invention, or fragments or variants thereof can also be assayed for their ability to neutralize, enhance, or not significantly alter, BLyS aetivity. For example, antibodies or fragments or variants thereof, may be routinely tested for their ability to inhibit BLyS from binding to cells expressing the receptor for BLyS (see Example 3, *infra*).

<u>Selection and Screening for Antibodies that Immunospecifically Bind to Soluble BLyS</u>

[0340] Antibodies of the invention (including scFvs and other molecules comprising, or alternatively eonsisting of, antibody fragments or variants thereof) may be screened in a variety of assays to identify those antibodies that immunospecifically bind to the soluble form of BLyS. In one particular assay, antibodies that bind to the biotinylated soluble form of BLyS in solution are captured on streptavidin eoated magnetic beads. This assay may be relatively applied to identify antibodies of the invention that neutralize and/or bind to BLyS. Additionally, antibodies may be assayed in neutralization assays described herein or otherwise known in the art (see Example 3, *infra*). For example, antibodies may be tested for their ability to inhibit soluble BLyS (e.g., biotinylated BLyS) from binding to IM9 cells. In this assay, labeled soluble BLyS (e.g., biotinylated BLyS) is incubated with candidate anti-BLyS antibodies to allow for the formation of BLyS -anti-BLyS antibody complexes. Following incubation, an aliquot of the BLyS-anti-BLyS antibody sample is added to IM9 cells. The binding of soluble BLyS may be determined using techniques known in the art. For example, the binding of biotinylated BLyS to IM9 cells may be detected using a fluorimeter following the addition of streptavidin-delfia. Biotinylated BLyS, if it is not bound by antibodies that neutralize BLyS, binds to the cells is detected.

Thus, an antibody that decreases the amount of bio-BLyS that binds to IM-9 cells (relative to a control sample in which the BLyS had been preincubated with an irrelevant antibody or no antibody at all) is identified as one that binds to and neutralizes the soluble form of BLyS. In another assay, antibodies are screened using ELISAs for those antibodies that bind to biotinylated soluble BLyS, but do not bind membrane-bound BLyS, such as, for example, BLyS on membranes from U937 cells (see Examples 2 and 9, *infra*). In these assays, soluble BLyS (e.g., biotinylated BLyS) and membrane-bound BLyS (e.g., on U937 membranes) are incubated in separate samples with the same antibodies and those antibodies that bind to the soluble BLyS (biotinylated BLyS), but not membrane-bound BLyS (e.g., on U937 membranes) are captured and identified.

[0341] Antibodies of the invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be tested to identify those antibodies that do not cross-react with APRIL, endokine-alpha, VEGI, TRAIL, TNF-alpha, TNF-beta, Fas-L, LIGHT, and PBS (see Example 4, *infra*). Antibodies may also be tested for their affinity for BLyS using, for example, BIAeore analysis (see Examples 6, 12, 17 and 18 *infra*). Antibodies may also be tested for their ability to stimulate, inhibit, or not alter, BLyS-induced immunoglobulin production and/or B-cell proliferation using techniques known to those of skill in the art. For example, human B-cells, BLyS and antibodies may be incubated together in 96 well plates and ^{3}H-thymidine incorporation may be measured using a scintillation counter.

<u>Selection and Screening for Antibodies that Immunospecifically Bind to Membrane-bound BLyS</u>

[0342] Antibodies of the invention (including scFvs and other molecules comprising, or alternatively eonsisting of, antibody fragments or variants thereof) may be screened in a variety of assays to identify those antibodies that immunospecifically bind to the membrane-bound form of BLyS. In one particular assay, antibodies that bind to BLyS on U937 membranes or immobilized histidine-tagged BLyS are captured. Other cell lines that express BLyS that might be useful for testing antibody binding to membrane-bound form of BLyS include, K-562, HL-60 and THP-1 cells. In another assay, antibodies are screened using ELISAs for those antibodies (or antibody fragments or variants) that bind to BLyS on U937 membranes or to histidine-tagged BLyS. In this assay, antibodies are

added to 96 well plates coated with U937 membranes or histidine-tagged BLyS and those antibodies or antibody fragments or variants that bind to the U937 membranes or histidine-tagged BLyS are captured. In another assay, antibodies are screened using ELISAs for those antibodies (or antibody fragments or variants thereof) that do not bind to biotinylated BLyS (soluble BLyS) but bind to membrane-bound BLyS, such as, for example, that on membranes from U937 cells (see Example 2, *infra*). In these assays, soluble BLyS (e.g., biotinylated BLyS) and membrane-bound BLyS (e.g., on U937 membranes) are incubated in separate samples with the same antibodies (or antibody fragments or variants) and those antibodies (or antibody fragments or variants) that do not bind to the soluble BLyS (biotinylated BLyS), but bind the membrane-bound BLyS (e.g., on U937 membranes) are captured and identified. In other assays, antibodies are screened using ELISAs to determine which of the antibodies (or antibody fragments or variants) that bind to histidine-tagged BLyS or membranes from U937 cells do not cross-react with APRIL, endokine-alpha, VEGI, TRAIL, TNF-alpha, TNF-beta, Fas-L, LIGHT, and PBS (See Example 4, *infra*). ELISAs can also be used to determine which of the antibodies (or antibody fragments or variants) that bind to histidine-tagged BLyS or membranes from U937 cells bind to BLyS in the presenee of TNF-alpha (see Example 4, *infra*). Antibodies or fragments or variants thereof that immunospecifically bind to the membrane-bound form of BLyS may also be tested for their affinity for histidine-tagged BLyS using high-throughput BIAcore analysis (see Example 14, *infra*).

[0343] Additionally, antibodies of the invention may be screened against cells engineered to express an "uneleavable" form of BLyS in order to determine their speeifieity for the membrane-bound form of BLyS. Mutations in BLyS which may achieve this result inelude, but are not limited to, the mutation or deletion of amino acid residues Lys-132 and/or Arg-133 of the BLyS sequence shown in SEQ ID NO:3228. A typical mutagenesis might include mutation of one or both of residues Lys-132 or Arg-133 to alanine residues. Cells expressing such an "uncleavable" form of BLyS provide a profound reagent to use in assaying the ability of antibodies to bind the membrane-bound form of BLyS.

<u>Selection and Screening for Antibodies that Immunospecifically Bind to Soluble and Membrane-bound BLyS</u>

[0344] Antibodies of the invention (including scFvs and other molecules comprising, or alternately consisting of, antibody fragments or variants) may be screened in a variety of assays to identify those antibodies or antibody fragments or variants that immunospecifically bind to the soluble form and membrane-bound form of BLyS. In one particular assay, antibodies that bind to immobilized BLyS are captured. In another assay, antibodies are screened using ELISAs for those antibodies (or antibody fragments or variants) that inhibit the binding of soluble BLyS (*e.g.* soluble bio-BLyS) to IM-9 cells as described *supra.* In other assays, antibodies are screened using ELISAs for those antibodies that bind to membranes from U937 cells. Additionally, further ELISA assays may be performed using techniques known in the art to determine which antibodies do not cross-react with APRIL, endokine-alpha, VEGI, TRAIL, TNF-alpha, TNF-beta, Fas-L, LIGHT, and PBS, or those antibodies that bind to BLyS in the presence of TNF-alpha (see Example 4 *infra*). Antibodies may be assayed in neutralization assays using techniques described herein or otherwise known in the art. Antibodies that immunospeeifieally bind to the soluble and membrane-bound forms of BLyS may also be tested for their affinity for BLyS using high-throughput BIAcore analysis.

Antibody Conjugates

[0345] The present invention encompasses antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), recombinantly fused or chemically conjugated (including both covalent and non-covalent conjugations) to a heterologous polypeptide (or portion thereof, preferably at least 10, at least 20, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90 or at least 100 amino acids of the polypeptide) to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through linker sequences. For example, antibodies of the invention may be used to target heterologous polypeptides to particular cell types (*e.g.*, cells of monocytic lineage and B-cells), either *in vitro* or *in vivo*, by fusing or conjugating the heterologous polypeptides to antibodies of the invention that are specific for particular cell surface antigens (e.g., membrane-bound BLyS on cells of monocytic lineage) or which bind antigens that bind particular cell surface receptors (e.g., TACI, BCMA, BAFF-R located on B cells). Antibodies fused or conjugated to heterologous polypeptides may also be used in *in vitro* immunoassays and purification

methods using methods known in the art. See *e.g.*, Harbor *et al.*, supra, and PCT publication WO 93/2 1232; EP 439,095; Naramura *et al.*, Immunol. Lett. 39:91-99 (1994); U.S. Patent 5,474,981; Gillies *et al.*, PNAS 89:1428-1432 (1992); Fell *et al.*, J. Immunol. 146:2446-2452 (1991), which are ineorporated by reference in their entireties.

[0346] In one embodiment, a fusion protein comprises a polypeptide having an amino acid sequence of any one of the VH domains referred to in Table 1, and a heterologous polypeptide. In another embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VH CDR1s referred to in Table 1, and a heterologous polypeptide. In another embodiment, a fusion protein eomprises a polypeptide having the amino acid sequence of any one of the VH CDR2s referred to in Table 1, and a heterologous polypeptide. In a preferred embodiment, a fusion protein comprises a polypeptide having the amino acid sequenee of any one of the VH CDR3s referred to in Table 1 (i.e., SEQ ID NOS:2129 - 3227), and a heterologous polypeptide.

[0347] In another embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VL domains referred to in Table 1, and a heterologous polypeptide. In another embodiment, a fusion protein comprises a polypeptide having the amino aeid sequence of any one of the VL CDR1s referred to in Table 1, and a heterologous polypeptide. In yet another embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VL CDR2s referred to in Table 1, and a heterologous polypeptide. In a preferred embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VL CDR3s referred to in Table 1, and a heterologous polypeptide.

[0348] In another embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VH domains referred to in Table 1, and one or more VL domains referred to in Table 1, and a heterologous polypeptide. In another embodiment, a fusion protein of the present invention comprises a polypeptide having the amino acid sequence of any one of the VH CDRs referred to in Table 1, and any one of the VL CDRs referred to in Table 1, and a heterologous polypeptide.

[0349] The present invention further includes compositions comprising, or alternatively consisting of, heterologous polypeptides fused or conjugated to antibody fragments. For example, the heterologous polypeptides may be fused or conjugated to a Fab fragment, Fd fragment, Fv fragment, $F(ab)_2$ fragment, or a portion thereof. Methods

for fusing or conjugating polypeptides to antibody portions are known in the art. See, *e.g.*, U.S. Patent Nos. 5,336,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851; 5,112,946; EP 307,434; EP 367,166; PCT publications WO 96/04388; WO 9 1/06570; Ashkenazi *et al.*, Proe. Natl. Acad. Sei. USA 88: 10535-10539 (1991); Zheng *et al.*, J. Immunol. 154:5590-5600 (1995); and Vil *et al.*, Proc. Natl. Aead. Sci. USA 89:11337- 11341 (1992) (said references ineorporated by reference in their entireties).

[0350] Additional fusion proteins of the invention may be generated through the teehniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to modulate the activities of antibodies (including scFvs and other molecules comprising , or alternatively consisting of, antibody fragments or variants thereof), such methods can be used to generate antibodies with altered activity (*e.g.*, antibodies with higher affinities and lower dissociation rates). See, generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten *et al.*, Curr. Opinion Biotechnol. 8:724-33 (1997); Harayama, Trends Bioteehnol. 16(2):76-82 (1998); Hansson, *et al.*, J. Mol. Biol. 287:265-76 (1999); and Lorenzo and Blasco, Biotechniques 24(2):308- 13 (1998) (each of these patents and publications are hereby incorporated by reference in its entirety). In one embodiment, polynueleotides encoding antibodies of the invention may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to reeombination. In another embodiment, one or more portions of a polynucleotide encoding an antibody whieh portions immunospecifically bind to BLyS may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

[0351] Moreover, the antibodies of the present invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), can be fused to marker sequences, such as a polypeptides to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine polypeptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz *et al.*, Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the hemagglutinin "HA"

tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson *et al.*, Cell 37:767 (1984)) and the "flag" tag (DYKDDDDK, (SEQ ID No: 3238) Stratagene, La Jolla, CA).

[0352] The present invention further encompasses antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example, monitor or prognose the development or progression of a tumor as part of a clinical testing procedure to, *e.g.*, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include, but are not limited to, various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Examples of suitable enzymes include, but are not limited to, horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include, but are not limited to, streptavidinlbiotin and avidin/biotin; examples of suitable fluorescent materials include, but are not limited to, umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes, but is not limited to, luminol; examples of bioluminescent materials include, but are not limited to, luciferase, luciferin, and aequorin; and examples of suitable radioactive material include, but are not limited to, iodine (^{131}I, ^{125}I, ^{123}I, ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{115m}In, ^{113m}In, ^{112}In, ^{111}In), and technetium (^{99}Tc, ^{99m}Tc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re, ^{188}Re, ^{142}Pr, ^{105}Rh, ^{97}Ru, ^{68}Ge, ^{57}Co, ^{65}Zn, ^{85}Sr, ^{32}P, ^{153}Gd, ^{169}Yb, ^{51}Cr, ^{54}Mn, ^{75}Se, ^{113}Sn, and ^{117}Tin.

[0353] Further, an antibody of the invention (including an scFv or other molecule comprising, or alternatively consisting of, antibody fragments or variants thereof), may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, ^{213}Bi. In specific embodiments, antibodies of the invention are attached to macrocyclic chelators useful for conjugating radiometal ions, including but not limited to, ^{111}In, ^{177}Lu, ^{90}Y, ^{166}Ho, and ^{153}Sm, to polypeptides. In preferred embodiments, the radiometal ion associated with the macrocyclic chelators attached to antibodies of the invention is ^{111}In. In preferred embodiments, the radiometal ion associated with the macrocyclic chelators attached to antibodies of the invention is ^{90}Y. In specific embodiments, the macrocyclic ehelator is 1,4,7,10-tetraazacyclododecane-N,N',N",N'"-tetraacetic acid (DOTA). In other specific embodiments, the DOTA is attached to the antibody of the invention via a linker molecule. Examples of linker molecules useful for conjugating DOTA to a polypeptide are commonly known in the art - see, for example, DeNardo et al., Clin Cancer Res. 4(10):2483-90, 1998; Peterson et al., Bioconjug. Chem. 10(4):553-7, 1999; and Zimmerman et al, Nucl. Med. Biol. 26(8):943-50, 1999 which are hereby incorporated by reference in their entirety.

[0354] A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells and includes such molecules as small molecule toxins and enzymatically active toxins of bacterial, fungal, plant, or animal origin, or fragments thereof. Examples include, but are not limited to, paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide (VP-16), tenoposide, vineristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, thymidine kinase, endonuclease, RNAse, and puromycin and frragments, variants or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (*e.g.*, methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (*e.g.*, mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cisdichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (*e.g.*, daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.*, dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin

(AMC)), and anti-mitotic agents (*e.g.*, vincristine and vinblastine), improsulfan, piposulfan, benzodopa, carboquone, meturedopa, uredopa, altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphaoramide trimethylolomelamine, chlornaphazine, cholophosphamide, estramustine, ifosfamide, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, chlorozotocin, fotemustine, nimustine, ranimustine, aclacinomysins, azaserine, cactinomycin, calichearnicin, carabicin, carminomycin, carzinophilin, chromomycins, detorubicin, 6-diazo-5-oxo-L-norleucine, epirubicin, esorubicin, idarubicin, marcellomycin, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, quelamycin, rodorubicin, streptonigrin, tubercidin, ubenimex, zinostatin, zorubicin, denopterin, pteropterin, trimetrexate, fludarabine, thiamiprine, ancitabine, azacitidine, 6-azauridine, carmofur, dideoxyuridine, doxifluridine, enocitabine, floxuridine, 5-FU, calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone, aminoglutethimide, mitotane, trilostane, frolinic acid, aceglatone, aldophosphamide glycoside, aminolevulinic acid, amsacrine, bestrabucil, bisantrene, edatraxate, defofamine, demecolcine, diaziquone, elfornithine, elliptinium acetate, etoglucid, gallium nitrate, hydroxyurea, lentinan, lonidamine, mitoguazone, mopidamol, nitracrine, pentostatin, phenamet, pirarubicin, podophyllinic acid, 2-ethylhydrazide, procarbazine, PSKO, razoxane, sizofiran, spirogermanium, tenuazonie acid, triaziquone, 2, 2',2''-trichlorotriethylamine, urethan, vindesine, dacarbazine, mannomustine, mitobronitol, mitolactol, pipobroman, gacytosine, arabinoside ("Ara-C"), taxoids, e.g. paclitaxel (TAXOL", Bristol-Myers Squibb Oncology, Princeton, NJ) doxetaxel (TAXOTERE", Rh6ne-Poulenc Rorer, Antony, France), gemcitabine, ifosfamide, vinorelbine, navelbine, novantrone, teniposide, aminopterin, xeloda, ibandronate, CPT-I 1, topoisomerase inhibitor RFS 2000, difluoromethylornithine (DMFO), retinoic acid, esperamicins, eapecitabine, and pharmaceutically acceptable salts, acids or derivatives of any of the above. Also ineluded in this definition are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens including for example tamoxifen, raloxifene, aromatase inhibiting 4(5)-imidazoles, 4 hydroxytamoxifen, trioxifene, keoxifene, LY 117018, onapristone, toremifene (Fareston), and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin, and pharmaceutically acceptable salts, acids or derivatives of any of the above.

[0355] Techniques known in the art may be applied to label antibodies of the invention. Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see e.g., U.S. Patent Nos. 5,756,065; 5,714,631; 5,696,239; 5,652,361; 5,505,931; 5,489,425; 5,435,990; 5,428,139; 5,342,604; 5,274,119; 4,994,560; and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety) and direct coupling reactions (e.g., Bolton-Hunter and Chloramine-T reaction).

[0356] The antibodies of the invention which are conjugates can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, but are not limited to, for example, a toxin such as abrin, ricin A, alpha toxin, pseudomonas exotoxin, or diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin; a protein such as tumor necrosis factor, alpha-interferon, beta-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, *e.g.*, TNF-alpha, TNF-beta, AIM I (see, International Publication No. WO 97/33899), AIM II (see, International Publication No. WO 97/34911), Fas Ligand (Takahashi *et al., Int. Immunol.,* 6:1567-1574 (1994)), VEGI (see, International Publication No. WO 99/23105), a thrombotic agent or an anti-angiogenic agent, *e.g.*, angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 (IL- 1), interleukin-2 (IL-2), interleukin-6 (IL-6), granulocyte macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), or other growth factors.

[0357] Antibodies of the invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

[0358] Techniques for conjugating a therapeutic moiety to antibodies are well known, see, *e.g.*, Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld *et al.* (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom *et al.*, "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson *et al.* (eds.), pp. 623-53 (Marcel Dekker,

Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinehera *et al.* (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin *et al.* (eds.), pp. 303-16 (Academic Press 1985), and Thorpe *et al.*, "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev. 62:119-58 (1982).

[0359] Alternatively, an antibody of the invention can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, which is incorporated herein by reference in its entirety.

[0360] An antibody of the invention (including an scFv or and other molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof), with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a therapeutic.

Use of Antibodies for Epitope Mapping

[0361] The present invention provides antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that can be used to identify epitopes of BLyS. In partieular, the antibodies of the present invention can be used to identify epitopes of human BLyS (SEQ ID NOS:3228 and/or 3229) or BLyS expressed on human monocytes; murine BLyS (SEQ ID NOS:3230 and/or 3231) or BLyS expressed on murine monocytes; rat BLyS (either the soluble forms as given in SEQ ID NOS:3232, 3233, 3234 and/or 3235 or in a membrane associated form, *e.g.*, on the surface of rat monocytes); or monkey BLyS (e.g., the monkey BLyS polypeptides of SEQ ID NOS:3236 and/or 3237, the soluble form of monkey BLyS, or BLyS expressed on monkey monocytes)using techniques described herein or otherwise known in the art. Fragments which function as epitopes may be produced by any conventional means. (See, *e.g.*, Houghten, Proc. Natl. Aead. Sci. USA 82:5131-5135 (1985), further described in U.S. Patent No. 4,631,211.)

Diagnostic Uses of Antibodies

[0362] Labeled antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) which specifically bind to BLyS can be used for diagnostic purposes to detect, diagnose, prognose, or monitor diseases and/or disorders associated with the aberrant expression and/or activity of BLyS or BLyS receptor. The invention provides for the detection of aberrant expression of BLyS comprising: (a) assaying the expression of BLyS in a biological sample from an individual using one or more antibodies of the invention that immunospecifically binds to BLyS; and (b) comparing the level of BLyS with a standard level of BLyS, *e.g.*, in normal biological samples, whereby an increase or decrease in the assayed level of BLyS compared to the standard level of BLyS is indicative of aberrant expression.

[0363] By "biological sample" is intended any fluids and/or cells obtained from an individual, body fluid, body tissue, body cell, cell line, tissue culture, or other source which may contain BLyS protein or mRNA. Body fluids include, but are not limited to, sera, plasma, urine, synovial fluid, spinal fluid, saliva, and mucous. Tissues samples may be taken from virtually any tissue in the body. Tissue samples may also be obtained from autopsy material. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

[0364] The invention also provides for the detection of aberrant expression of BLyS receptor comprising (a) assaying the expression of BLyS receptor in a biological sample from an individual using one or more antibodies or fragments or variants thereof that immunospecifically binds only to soluble BLyS, but does not inhibit BLyS /BLyS receptor binding. Such an antibody, by way of an example that is not to be construed as limiting, would bc one that is able to capture a biotinylated BLyS from solution (see Example 8), but that would not prevent BLyS from binding to IM-9 cells (see Example 3). and (b) comparing the level of BLyS receptor with a standard level of BLyS receptor, *e.g.*, in normal tissue or cell samples, whereby an increase or decrease in the assayed level of BLyS receptor compared to the standard level of BLyS receptor is indicative of aberrant expression.

[0365] Antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) which specifically bind to BLyS can be used for diagnostic purposes to detect, diagnose, prognose, or monitor autoimmune

disorders and/or immunodeficiencies, and/or diseases or conditions associated therewith. The invention provides for the detection of aberrant expression of BLyS comprising: (a) assaying the expression of BLyS in a biological sample from an individual using one or more antibodies of the invention that immunospecifically binds to BLyS; and (b) comparing the level of BLyS with a standard level of BLyS, *e.g.*, in normal biological samples, whereby an increase or decrease in the assayed level of BLyS compared to the standard level of BLyS is indicative of an autoimmune disorder or disease and/or an immunodeficiency. In specific embodiments, an increase in the assayed level of BLyS is indicative of an autoimmune disorder or disease. In other specific embodiments, a decrease in the assayed level of BLyS is indicative of an immunodeficiency.

[0366] Antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) which specifically bind to BLyS but, do not inhibit BLyS/BLyS receptor binding can be used for diagnostic purposes to detect, diagnose, prognose, or monitor autoimmune disorders and/or immunodeficiencies, and/or diseases or conditions associated therewith. The invention provides for the detection of aberrant expression of BLyS receptor comprising: (a) assaying the expression of BLyS receptor in a biological sample from an individual using one or more antibodies of the invention that immunospeeifically binds to BLyS; and (b) comparing the level of BLyS receptor with a standard level of BLyS reeeptor, *e.g.*, in normal biological samples, whereby an increase or decrease in the assayed level of BLyS receptor compared to the standard level of BLyS receptor is indicative of an autoimmune disorder or disease and/or an immunodeficiency. In specific embodiments, an increase in the assayed level of BLyS receptor is indicative of an autoimmune disorder or disease. In other speeific embodiments, a decrease in the assayed level of BLyS receptor is indicative of an immunodeficiency.

[0367] Autoimmune disordcrs, diseases, or conditions that may be detected, diagnoscd, prognosed, or monitored using the antibodies of the invention inelude, but are not limited to, autoimmune hemolytic anemia, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura, autoimmune neutropenia, autoimmunocytopenia, hemolytic anemia, antiphospholipid syndrome, dermatitis, gluten-sensitive enteropathy, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart disease, glomerulonephritis (e.g., IgA nephropathy), Multiple Sclerosis, Neuritis, Uveitis

Ophthalmia, Polyendocrinopathies, Purpura (e.g., Henloch-Scoenlein purpura), Reiter's Disease, Stiff-Man Syndrome, Autoimmune Pulmonary Inflammation, myocarditis, IgA glomerulonephritis, dense deposit disease, rheumatic heart disease, Guillain-Barre Syndrome, diabetes mellitus *(e.g.* Type I diabetes mellitus or insulin dependent diabetes mellitis), juvenile onset diabetes, and autoimmune inflammatory eye, autoimmune thyroiditis, hypothyroidism (i.e., Hashimoto's thyroiditis, systemic lupus erhythematosus, discoid lupus, Goodpasture's syndrome, Pemphigus, Receptor autoimmunities such as, for example, (a) Graves' Disease , (b) Myasthenia Gravis, and (c) insulin resistance, autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura, rheumatoid arthritis, schleroderma with anti-collagen antibodies, mixed connective tissue disease, polymyositis/dermatomyositis, pernicious anemia (Addison's disease), idiopathic Addison's disease, infertility, glomerulonephritis such as primary glomerulonephritis and IgA nephropathy, bullous pemphigoid, Sjögren's syndrome, diabetes millitus, and adrenergie drug resistanee (including adrenergic drug resistance with asthma or cystic fibrosis), chronic active hepatitis, primary biliary cirrhosis, other endocrine gland failure, vitiligo, vasculitis, post-MI, eardiotomy syndrome, urticaria, atopic dermatitis, asthma, inflammatory myopathies, and other inflammatory, granulomatous, degenerative, and atrophic disorders and other disorders sueh as inflammatory skin diseases ineluding psoriasis and sclerosis, responses assoeiated with inflammatory bowel disease (such as Crohn's disease and uleerative colitis), respiratory distress syndrome (including adult respiratory distress syndrome, ARDS), meningitis, eneephalitis, colitis, allergie conditions such as eczema and other conditions involving infiltration of T cells and chronic inflammatory responses, atherosclerosis, leukocyte adhesion deficiency, Reynaud's syndrome, and immune responses associated with acute and delayed hypersensitivity mediated by eytokines and T-lymphocytes typically found in tuberculosis, sarcoidosis, granulomatosis and diseases involving leukoeyte diapedesis, central nervous system (CNS) inflammatory disorder, multiple organ injury syndrome, antigen-antibody complex mediated diseases, anti-glomerular basement membrane disease, Lambert-Eaton myasthenic syndrome, Beheet disease, giant cell arteritis, immune complex nephritis, IgA nephropathy, IgM polyneuropathies or autoimmune thrombocytopenia etc.

[0368] In specific embodiments, the present invention encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders associated

with hypergammaglobulinemia (e.g., AIDS, autoimmune diseases, and some immunodeficiencies). In other specific embodiments, the present invention encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders associated with hypogammaglobulinemia (e.g., an immunodeficiency).

[0369] Immunodeficiencies that may be detected, diagnosed, prognosed, or monitored using the antibodies of the invention include, but are not limited to, severe combined immunodeficiency (SCID)-X linked, SCID-autosomal, adenosine deaminase deficiency (ADA deficiency), X-linked agammaglobulinemia (XLA), Bruton's disease, congenital agammaglobulinemia, X-linked infantile agammaglobulinemia, acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, transient hypogammaglobulinemia of infancy, unspecified hypogammaglobulinemia, agammaglobulinemia, common variable immunodeficiency (CVID) (acquired), Wiskott-Aldrich Syndrome (WAS), X-linked immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, selective IgA deficiency, IgG subclass deficiency (with or without IgA deficiency), antibody deficiency with normal or elevated Igs, immunodeficiency with thymoma, Ig heavy chain deletions, kappa chain deficiency, B cell lymphoproliferative disorder (BLPD), selective IgM immunodeficiency, recessive agammaglobulinemia (Swiss type), reticular dysgenesis, neonatal neutropenia, severe congenital leukopenia, thymic alymphoplasia-aplasia or dysplasia with immunodeficiency, ataxia-telangiectasia, short limbed dwarfism, X-linked lymphoproliferative syndrome (XLP), Nezelof syndrome-combined immunodeficiency with Igs, purine nucleoside phosphorylase deficiency (PNP), MHC Class II deficiency (Bare Lymphocyte Syndrome) and severe combined immunodeficiency.

[0370] Elevated levels of soluble BLyS have been observed in the serum of patients with Systemic Lupus Erythematosus (SLE). In comparing the sera of 150 SLE patients with that of 38 control individuals, it was found that most of the SLE patients had more than 5ng/ml of serum BLyS, more than 30% of SLE patients had levels greater than 10ng/ml, and approximately 10% of SLE patients had serum BLyS levels greater than 20ng/ml. In contrast, the majority of normal controls had BLyS levels less than 5ng/ml, and less than 10% had levels higher than 10ng/ml. The elevated levels of BLyS protein in sera is present in the soluble form and has biologic activity as assayed by the ability to

stimulate anti-IgM treated B cells in vitro. SLE patients with more than 15ng/ml serum BLyS were also found to have elevated levels of anti-dsDNA antibodies compared to both normal controls and SLE patients with less than 5ng/ml of serum BLyS.(unpublished data).

[0371] In addition the serum of two subgroups of patients which were positive for anti-nuclear antibodies (ANA+) but did not meet the formal requirements of the American College of Rheumatology (ACR) for classification of SLE were analyzed for BLyS levels. The first subgroup of sera was ANA+ sera that came from patients who did not present with the clinical impression of SLE. This group had only slightly elevated levels of BLyS (~9ng/ml BLyS). The second subgroup however, which was ANA+ sera from patients who presented with the clinical impression of SLE, had significantly increased BLyS levels (~15ng/ml). These results suggest that an elevated level of BLyS precedes the formal fulfillment of the ACR criteria. The ACR criteria are described in Tan, E.M., et al, *Arthritis and Rheumatism* 25:1271 – 1277 (1982).

[0372] Thus in specific embodiments, antibodies of the invention which specifically bind to BLyS can be used for diagnostic purposes to detect, diagnose, prognose, or monitor Systemic Lupus Erythematosus or conditions associated therewith. The invention provides for the detection of aberrant expression of BLyS comprising: (a) assaying the expression of BLyS in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to BLyS; and (b) comparing the level of BLyS with a standard level of BLyS, *e.g.*, in normal biological samples, whereby an increase in the assayed level of BLyS compared to the standard level of BLyS is indicative of SLE.

[0373] In other specific embodiments, antibodies of the invention which specifically bind to BLyS can be used for diagnostie purposes to detect, diagnose, prognose, or monitor IgA nephropathy or conditions associated therewith. The invention provides for the detection of aberrant expression of BLyS comprising: (a) assaying the expression of BLyS in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to BLyS; and (b) comparing the level of BLyS with a standard level of BLyS, *e.g.*, in normal biologieal samples, whereby an increase in the assayed level of BLyS compared to the standard level of BLyS is indicative of IgA nephropathy.

[0374] In other specific embodiments, antibodies of the invention which specifically bind to BLyS can be used for diagnostic purposes to detect, diagnose, prognose, or monitor Sjögren's Syndrome or conditions associated therewith. The invention provides for the detection of aberrant expression of BLyS comprising: (a) assaying the expression of BLyS in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to BLyS; and (b) comparing the level of BLyS with a standard level of BLyS, *e.g.*, in normal biological samples, whereby an increase in the assayed level of BLyS compared to the standard level of BLyS is indicative of Sjögren's Syndrome.

[0375] In other specific embodiments, antibodies of the invention which specifically bind to BLyS can be used for diagnostic purposes to detect, diagnose, prognose, or monitor HIV infeetion or conditions associated therewith (e.g. AIDS). The invention provides for the detection of aberrant expression of BLyS comprising: (a) assaying the expression of BLyS in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to BLyS; and (b) comparing the level of BLyS with a standard level of BLyS, *e.g.*, in normal biological samples, whereby an increase in the assayed level of BLyS compared to the standard level of BLyS is indicative of HIV infection.

[0376] In other specific embodiments, antibodies of the invention which specifically bind to BLyS ean be used for diagnostic purposes to detect, diagnose, prognose, or monitor Myasthenia Gravis or conditions assoeiated therewith. The invention provides for the detection of aberrant expression of BLyS eomprising: (a) assaying the expression of BLyS in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to BLyS; and (b) comparing the level of BLyS with a standard level of BLyS, *e.g.*, in normal biological samples, whereby an increase in the assayed level of BLyS compared to the standard level of BLyS is indicative of Myasthenia Gravis.

[0377] In other specifie embodiments, antibodies of the invention which specifically bind to BLyS can be used for diagnostic purposes to detect, diagnose, prognose, or monitor idiopathic thrombocytopenic purpura (ITP) or conditions associated therewith. The invention provides for the detection of aberrant expression of BLyS comprising: (a) assaying the expression of BLyS in a biological sample of an individual using one or more

antibodies of the invention that immunospecifically binds to BLyS; and (b) comparing the level of BLyS with a standard level of BLyS, *e.g.*, in normal biological samples, whereby an increase in the assayed level of BLyS compared to the standard level of BLyS is indicative of idiopathic thrombocytopenic purpura (ITP).

[0378] In other specific embodiments, antibodies of the invention which specifically bind to BLyS can be used for diagnostic purposes to detect, diagnose, prognose, or monitor hemolytic anemia or conditions associated therewith. The invention provides for the detection of aberrant expression of BLyS comprising: (a) assaying the expression of BLyS in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to BLyS; and (b) comparing the level of BLyS with a standard level of BLyS, *e.g.*, in normal biological samples, whereby an increase in the assayed level of BLyS compared to the standard level of BLyS is indicative of hemolytic anemia.

[0379] In other specific embodiments, antibodies of the invention which specifically bind to BLyS can be used for diagnostic purposes to detect, diagnose, prognose, or monitor thyroiditis or conditions associated therewith. The invention provides for the detection of aberrant expression of BLyS comprising: (a) assaying the expression of BLyS in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to BLyS; and (b) comparing the level of BLyS with a standard level of BLyS, *e.g.*, in normal biological samples, whereby an increase in the assayed level of BLyS compared to the standard level of BLyS is indicative of thyroiditis.

[0380] In other specific embodiments, antibodies of the invention which specifically bind to BLyS can be used for diagnostic purposes to detect, diagnose, prognose, or monitor Goodpasture's syndrome or conditions associated therewith. The invention provides for the detection of aberrant expression of BLyS comprising: (a) assaying the expression of BLyS in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to BLyS; and (b) comparing the level of BLyS with a standard level of BLyS, *e.g.*, in normal biological samples, whereby an increase in the assayed level of BLyS compared to the standard level of BLyS is indicative of Goodpasture's syndrome.

[0381] In other specific embodiments, antibodies of the invention which specifically bind to BLyS can be used for diagnostic purposes to detect, diagnose, prognose, or

monitor multiple sclerosis or conditions associated therewith. The invention provides for the detection of aberrant expression of BLyS comprising: (a) assaying the expression of BLyS in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to BLyS; and (b) comparing the level of BLyS with a standard level of BLyS, *e.g.*, in normal biological samples, whereby an increase in the assayed level of BLyS compared to the standard level of BLyS is indicative of multiple sclerosis.

[0382] In additional embodiments, antibodies of the invention which specifically bind to BLyS can be used for diagnostic purposes to detect, diagnose, prognose, or monitor Rheumatoid Arthritis. The invention provides for the detection of aberrant expression of BLyS comprising: (a) assaying the expression of BLyS in a biological sample (e.g., serum and synovial fluid) of an individual using one or more antibodies of the invention that immunospecifically binds to BLyS; and (b) comparing the level of BLyS with a standard level of BLyS, *e.g.*, in normal biological samples, whereby an increase in the assayed level of BLyS compared to the standard level of BLyS is indicative of Rheumatoid arthritis.

[0383] In additional embodiments, antibodies of the invention which specifically bind to BLyS can be used for diagnostic purposes to detect, diagnose, prognose, or monitor an immune-based rheumatologic disease, (e.g., SLE, rheumatoid arthritis, CREST syndrome (a variant of scleroderma characterized by calcinosis, Raynaud's phenomenon, esophageal motility disorders, sclerodactyly, and telangiectasia.), Seronegative spondyloarthropathy (SpA), Polymyositis/dermatomyositis, Microscopic polyangiitis, Hepatitis C-associated arthritis, Takayasu's arteritis, and undifferentiated connective tissue disorder). The invention provides for the detection of aberrant expression of BLyS comprising: (a) assaying the expression of BLyS in a biological sample (e.g., serum and synovial fluid) of an individual using one or more antibodies of the invention that immunospecifically binds to BLyS; and (b) comparing the level of BLyS with a standard level of BLyS, *e.g.*, in normal biological samples, whereby an increase in the assayed level of BLyS eompared to the standard level of BLyS is indicative of monitor an immune-based rheumatologic disease.

[0384] It has been observed, that serum BLyS levels inversely correlate with nephrotic range proteinuria (>3gm proteinuria in a 24 hour urine collection) using a sample of 71 SLE patients (p=0.019). Proteinuria was determined in 71 SLE patients within one month

of phlebotomy for serum BLyS determination. Serum BLyS was classified as low, normal, or high based on the 5th through 95th percentiles for normal controls. Nephrotic-range proteinuria was inversely correlated with serum Neutrokine-alpha levels. Thus, in specific embodiments, serum levels of BLyS (determined using one or more antibodies of the present invention) in individuals diagnosed with an immune based rheumatologic disease (e.g., SLE, rheumatoid arthritis, CREST syndrome (a variant of scleroderma characterized by calcinosis, Raynaud's phenomenon, esophageal motility disorders, sclerodactyly, and telangiectasia.), seronegative spondyloarthropathy (SpA), polymyositis/dermatomyositis, microscopic polyangiitis, hepatitis C-asociated arthritis, Takayasu's arteritis, and undifferentiated conneetive tissue disorder) may be used to determine, diagnose, prognose, or monitor the severity of certain aspects or symptoms of the disease, such as nephrotic-range proteinuria.

[0385] In another specific embodiment, antibodies of the invention are used to diagnose, prognose, treat, or prevent conditions associated with CVID, including, but not limited to, conditions associated with acute and recurring infections (e.g., pneumonia, bronchitis, sinusitis, otitis media, sepsis, meningitis, septic arthritis, and osteomyelitis), chronic lung disease, autoimmunity, granulomatous disease, lymphoma, cancers (e.g., cancers of the breast, stomach, colon, mouth, prostate, lung, vagina, ovary, skin, and melanin forming cells (i.e. melanoma), inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis, and ulcerative proctitis), malabsorption, Hodgkin's disease, and Waldenstrom's macroglobulinemia.

[0386] The invention provides a diagnostic assay for diagnosing or prognosing a disease or disorder, comprising: (a) assaying for the level of BLyS in a biological sample of an individual using one or more antibodies of the invention that immunospecifically bind to BLyS; and (b) comparing the level of BLyS with a standard BLyS level, *e.g.*, in a biological sample from a patient without the disease or disorder, whereby an increase or decrease in the assayed BLyS level compared to the standard level of BLyS is indicative of a particular disease or disorder. With respect to cancer, the presence of a relatively high amount of BLyS in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may

allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

[0387] In specific embodiments, the presence of a relatively high amount of membrane-bound BLyS in a biological sample is indicative of monocytic cell related leukemias or lymphomas, such as, for example acute myelogenous leukemia and/or the severity thereof.

[0388] In other specific embodiments, the presence of a relatively high amount of BLyS receptor in a biological sample (as determined using antibodies of the invention that bind to soluble BLyS, but do not inhibit BLyS/BLyS receptor binding) is indicative of B cell related leukemias or lymphomas (e.g., chronic lymphocytic leukemia, multiple myeloma, non-Hodgkin's lymphoma, and Hodgkin's disease), and/or the severity thereof.

[0389] In specific embodiments, the invention provides a diagnostic assay for diagnosing or prognosing Systemic Lupus Erythematosus, eomprising: (a) assaying for the level of BLyS in a biological sample of an individual using one or more antibodies of the invention that immunospecifically bind to BLyS; and (b) comparing the level of BLyS with a standard BLyS level, *e.g.*, in a biological sample from a patient without Systemic Lupus Erythematosus, whereby an increase in the assayed BLyS level compared to the standard level of BLyS is indieative of Systemic Lupus Erythematosus.

[0390] In specific embodiments, the invention provides a diagnostic assay for diagnosing or prognosing a Rheumatoid Arthritis, comprising: (a) assaying for the level of BLyS in a biological sample of an individual using one or more antibodies of the invention that immunospecifically bind to BLyS; and (b) comparing the level of BLyS with a standard BLyS level, *e.g.*, in a biological sample from a patient without Rheumatoid Arthritis, whereby an increase or decrease in the assayed BLyS level compared to the standard level of BLyS is indicative of Rheumatoid Arthritis.

[0391] The invention provides a diagnostie assay for diagnosing or prognosing a disease or disorder, comprising: (a) assaying for the level of BLyS receptor in cells or a tissue sample of an individual using one or more antibodies of the invention that immunospecifically binds only to soluble BLyS, but does not neutralize BLyS /BLyS receptor binding; and (b) comparing the level of BLyS receptor with a standard BLyS receptor level, *e.g.*, in a tissue sample from a patient without the disease or disorder, whereby an increase or decrease in the assayed BLyS receptor level compared to the

standard level of BLyS receptor is indicative of a particular disease or disorder. With respect to cancer, the presence of a relatively high amount of BLyS receptor in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

[0392] Antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) can be used to assay protein levels in a biological sample using classical immunohistological methods as described herein or as known to those of skill in the art (*e.g.*, see Jalkanen, *et al.*, J. Cell. Biol. 101:976-985 (1985); Jalkanen, *et al.*, J. Cell . Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, alkaline phosphatase, and horseradish peroxidase; radioisotopes, such as iodine (^{121}I, ^{123}I, ^{125}I, ^{131}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{111}In, ^{112}In, ^{113m}In, ^{115m}In), technetium (^{99}Tc,^{99m}Tc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re, ^{188}Re, ^{142}Pr, ^{105}Rh, and ^{97}Ru; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0393] One aspect of the invention is the detection and diagnosis of a disease or disorder associated with aberrant expression of BLyS or BLyS receptor in an animal, preferably a mammal and most preferably a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled antibody of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically binds to BLyS; b) waiting for a time interval following the administering for permitting the labeled antibody to preferentially concentrate at sites in the subject where BLyS is expressed (and for unbound labeled molecule to be cleared to background level); e) determining background level; and d) detecting the labeled antibody in the subjeet, sueh that detection of labeled antibody or

fragment thereof above the background level and above or below the level observed in a person without the disease or disorder indicates that the subject has a particular disease or disorder associated with aberrant expression of BLyS or BLyS receptor. Background level can be determined by various methods including, comparing the amount of labeled molecule detected to a standard value previously determined for a particular system.

[0394] It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of ^{99}Tc. The labeled antibody will then preferentially accumulate at the location of cells which contain the specific protein. *In vivo* tumor imaging is described in S.W. Burchiel *et al.*, "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).

[0395] Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

[0396] In an embodiment, monitoring of the disease or disorder is carried out by repeating the method for diagnosing the disease or disorder, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

[0397] Presence of the labeled molecule can be detected in the patient using methods known in the art for *in vivo* scanning. These methods depend upon the type of label used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

[0398] In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston *et al.*,

U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patient using positron emission-tomography. In yet another embodiment, the molecule is labeled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI).

Immunophenotyping

[0399] The antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be utilized for immunophenotyping of cell lines and biological samples by their BLyS expression or BLyS receptor expression. Various techniques can be utilized using antibodies, fragments, or variants of the invention to screen for cellular populations (*i.e.*, immune cells, particularly monocytic cells or B-cells) expressing BLyS or BLyS receptor, and include magnetic separation using antibody-coated magnetic beads, "panning" with antibody attaehed to a solid matrix (*i.e.*, plate), and flow cytometry (see, *e.g.*, U.S. Patent 5,985,660; and Morrison *et al.*, Cell, 96:737-49 (1999)).

[0400] These techniques allow for the screening of particular populations of eells, such as might be found with hematological malignancies (*i.e.*, minimal residual disease (MRD) in acute leukemic patients) and "non-self" cells in transplantations to prevent Graft-versus-Host Disease (GVHD). Alternatively, these techniques allow for the screening of hematopoietic stem and progenitor cells capable of undergoing proliferation and/or differentiation, as might be found in human umbilical cord blood.

[0401] In one embodiment, antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) are used to identify cells of monocytic or B cell origin.

Therapeutic Uses of Antibodies

[0402] The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the disclosed

diseases, disorders, or conditions. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention and nucleic acids encoding antibodies (and anti-idiotypic antibodies) of the invention as described herein. The antibodies of the invention can be used to treat, ameliorate or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of BLyS or BLyS receptor, including, but not limited to, any one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or conditions associated with aberrant BLyS expression and/or activity or aberrant BLyS receptor expression and/or activity includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

[0403] Antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that function as agonists or antagonists of BLyS, preferably of BLyS-induced signal transduction, can be administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant BLyS expression, lack of BLyS function, aberrant BLyS receptor expression, or lack of BLyS receptor function. For example, antibodies of the invention whieh disrupt the interaction between BLyS and its receptor may be administered to an animal to treat, prevent or ameliorate a disease or disorder assoeiated with aberrant BLyS expression, excessive BLyS function, aberrant BLyS receptor expression, or exeessive of BLyS reeeptor function. Antibodies of the invention which do not prevent BLyS from binding its receptor but inhibit or downregulate BLyS-induced signal transduction can be administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant BLyS expression, excessive BLyS function, aberrant BLyS receptor expression, or excessive BLyS receptor function. In particular, antibodies of the present invention which prevent BLyS-induced signal transduetion by specifically recognizing the unbound BLyS, receptor-bound BLyS or both unbound and receptor-bound BLyS ean be administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant BLyS expression, excessive BLyS function, aberrant BLyS receptor expression, or excessive BLyS receptor function. The ability of an antibody of the invention to inhibit or downregulate BLyS-induced signal transduction may be determined by techniques described herein or otherwise known in the art. For example, BLyS-

induced receptor activation and the activation of signaling molecules can be determined by detecting the phosphorylation (*e.g.*, tyrosine or serine/threonine) of the receptor or a signaling molecule by immunoprecipitation followed by western blot analysis (for example, as described herein).

[0404] In a specific embodiment, an antibody of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that inhibits or downregulates BLyS activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, at least 50%, at least 45%, at least 40%, at least 45%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10% relative to BLyS activity in absence of the antibody is administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant BLyS expression, excessive BLyS function, aberrant BLyS receptor expression, or excessive BLyS receptor function. In another embodiment, a combination of antibodies, a eombination of antibody fragments, a eombination of antibody variants, or a combination of antibodies, antibody fragments, and/or variants that inhibit or downregulate BLyS activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, at least 50%, at least 45%, at least 40%, at least 45%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10% relative to BLyS activity in absence of said antibodies, antibody fragments, and/or antibody variants are administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant BLyS expression, excessive BLyS function, aberrant BLyS receptor expression, or excessive BLyS receptor function.

[0405] Further, antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) which activate BLyS-induced signal transduction can be administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant BLyS expression, lack of BLyS function, aberrant BLyS receptor expression, or lack of BLyS receptor function. These antibodies may potentiate or activate either all or a subset of the biological activities of BLyS-mediated receptor activation, for example, by inducing multimerization of BLyS and/or multimerization of the receptor. The antibodies of the invention may be administered with or without being pre-complexed with BLyS. In a specific embodiment, an antibody of the present invention that increases BLyS activity by at least 5%, at least

10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% relative to BLyS activity in absence of the antibody is administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant BLyS expression, lack of BLyS function, aberrant BLyS receptor expression, or lack of BLyS receptor function. In another embodiment, a combination of antibodies, a combination of antibody fragments, a combination of antibody variants, or a combination of antibodies, antibody fragments and/or antibody variants that increase BLyS activity by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% relative to BLyS activity in absence of the said antibodies or antibody fragments and/or antibody variants is administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant BLyS expression or lack of BLyS function or aberrant BLyS receptor expression or lack of BLyS receptor function.

[0406] One or more antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to BLyS may be used locally or systemically in the body as a therapeutic. The antibodies of this invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may also be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, *e.g.*, IL-2, IL-3 and IL-7), for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

[0407] The antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be administered alone or in combination with other types of treatments (*e.g.*, radiation therapy, chemotherapy, hormonal therapy, immunotherapy, anti-tumor agents, anti-angiogenesis and anti-inflammatory agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, human antibodies, fragments, or

variants, (e.g., derivatives), or nucleic acids, are administered to a human patient for therapy or prophylaxis.

[0408] It is preferred to use high affinity and/or potent *in vivo* inhibiting and/or neutralizing antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to BLyS, or polynucleotides encoding antibodies that immunospecifically bind to BLyS, for both immunoassays directed to and therapy of disorders related to BLyS polynucleotides or polypeptides, including fragments thereof. Such antibodies will preferably have an affinity for BLyS and/or BLyS fragments. Preferred binding affinities include those with a dissoeiation constant or K_D less than or equal to 5 X 10^{-2} M, 10^{-2} M, 5 X 10^{-3} M, 10^{-3} M, 5 X 10^{-4} M, 10^{-4} M, 5 X 10^{-5} M, or 10^{-5} M. More preferably, antibodies of the invention bind BLyS polypeptides or fragments or variants thereof with a dissociation constant or K_D less than or equal to 5 X 10^{-6} M, 10^{-6} M, 5 X 10^{-7} M, 10^{-7} M, 5 X 10^{-8} M, or 10^{-8} M. Even more preferably, antibodies of the invention bind BLyS polypeptides or fragments or variants thereof with a dissociation eonstant or K_D less than or equal to 5 X 10^{-9} M, 10^{-9} M, 5 X 10^{-10} M, 10^{-10} M, 5 X 10^{-11} M, 10^{-11} M, 5 X 10^{-12} M, 10^{-12} M, 5 X $^{-13}$ M, 10^{-13} M, 5 X 10^{-14} M, 10^{-14} M, 5 X 10^{-15} M, or 10^{-15} M. The invention eneompasses antibodies that bind BLyS polypeptides with a dissociation constant or K_D that is within any one of the ranges that are between eaeh of the individual reeited values.

[0409] In a preferred embodiment, antibodies of the invention neutralize BLyS aetivity. In another preferred embodiment, antibodies of the invention inhibit B cell proliferation.

[0410] In a preferred embodiment, antibodies of the invention (ineluding moleeules comprising, or alternatively consisting of, antibody fragments or variants thereof) inhibit or reduee binding of the soluble form of BLyS to a BLyS receptor. In another preferred embodiment antibodies of the invention inhibit or reduce B eell proliferation induced by the soluble form of BLyS. In another preferred embodiment antibodies of the invention inhibit or reduce immunoglobulin produetion induced by the soluble form of BLyS.

[0411] In a preferred embodiment, antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) inhibit or reduce binding of membrane-bound BLyS to a BLyS receptor. In another preferred embodiment, antibodies of the invention inhibit or reduce B cell proliferation induced by

the membrane-bound form of BLyS. In another preferred embodiment, antibodies of the invention inhibit or reduce immunoglobulin production induced by the membrane bound form of BLyS.

[0412] In a preferred embodiment, antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) inhibit or reduce binding of both the soluble and membrane-bound forms of BLyS to a BLyS receptor. In another preferred embodiment, antibodies of the invention inhibit or reduce B cell proliferation induced by either or both forms of BLyS. In another preferred embodiment, antibodies of the invention inhibit or reduce immunoglobulin production induced by either or both forms of BLyS.

[0413] In one embodiment, the invention provides a method of delivering antibody conjugates of the invention to targeted cells, such as, for example, monocytic cells expressing the membrane-bound form of BLyS, or B cells expressing a BLyS receptor.

[0414] In one embodiment, the invention provides a method for the specific delivery of antibodies and antibody conjugates of the invention to cells by administering molecules of the invention that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutie protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nueleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

[0415] In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering antibodies or antibody eonjugates of the invention (e.g., antibodies conjugated with radioisotopes, toxins, or cytotoxic prodrugs).In a specific embodiment, the invention provides a method for the specifie destruction of cells of monocytic lineage (e.g., monocytic cell related leukemias or lymphomas, such as, for example acute myelogenous leukemia) by administering antibodies or antibody conjugates of the invention (e.g., antibodies conjugated with radioisotopes, toxins, or cytotoxic prodrugs) that immunospecifically bind the membrane-bound form of BLyS. In another specific embodiment, the invention provides a method for the specific destruction of cells of B cell lineage (e.g., B cell related leukemias or lymphomas (e.g., chronic lymphocytic leukemia, multiple myeloma, non-

Hodgkin's lymphoma, and Hodgkin's disease) by administering antibodies or antibody conjugates of the invention (e.g., antibodies conjugated with radioisotopes, toxins, or cytotoxic prodrugs) that bind soluble BLyS, but do not inhibit BLyS binding to a BLyS receptor on B cells.

[0416] In another preferred embodiment antibodies of the invention (including antibody fragments and variants) promote or enhance B cell proliferation induced by the soluble form of BLyS. In another preferred embodiment, antibodies of the invention (including antibody fragments and variants) promote or enhance B cell proliferation induced by the membrane or soluble form of APRIL. In another preferred embodiment antibodies of the invention (including antibody fragments and variants) increase or enhance immunoglobulin production induced by the soluble form of BLyS. In another preferred embodiment antibodies of the invention (including antibody fragments and variants) increase or enhanee immunoglobulin production induced by the membrane bound or soluble form of APRIL. In another preferred embodiment antibodies of the invention (including antibody fragments and variants) increase or enhance immunoglobulin production in response to T cell dependent immunogens. In another preferred embodiment antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhanee immunoglobulin production in response to T cell independent immunogens.

[0417] In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate immune disorders. Immune disorders include, but are not limited to, autoimmune disorders (*e.g.*, arthritis, graft rejection, Hashimoto's thyroiditis, insulin-dependent diabetes, lupus, idiopathic thrombocytopenic purpura, systemic lupus erythrematosus and multiple sclerosis), elective IgA deficiency, ataxia-telangiectasia, common variable immunodefieiency (CVID), X-linked agammaglobulinemia, severe combined immunodeficiency (SCID), Wiskott-Aldrich syndrome, idiopathie hyper-eosinophilic syndrome, monocytic leukemoid reaction, monocytic leukocytosis, monoeytic leukopenia, monocytopenia, monocytosis, and graft or transplant rejection.

[0418] As discussed herein, antibodies and antibody eompositions of the invention, may be used to treat, prevent, ameliorate, diagnose or prognose various immune system-related disorders and/or conditions associated with these disorders, in mammals,

preferably humans. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of antibody and antibody compositions of the invention that can inhibit an immune response, particularly the proliferation of B cells and/or the production of immunoglobulins, may be an effective therapy in treating and/or preventing autoimmune disorders. Thus, in preferred embodiments, antibodies and antibody compositions of the invention are used to treat, prevent, ameliorate, diagnose and/or prognose an autoimmune disorder, or condition(s) associated with such disorder.

[0419] Autoimmune disorders and conditions associated with these disorders that may be treated, prevented, ameliorated, diagnosed and/or prognosed with the therapeutic and pharmaeeutical compositions of the invention include, but are not limited to, autoimmune hemolytic anemia, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura, autoimmune neutropenia, autoimmunocytopenia, hemolytic anemia, antiphospholipid syndrome, dermatitis, gluten-sensitive enteropathy, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart disease, glomerulonephritis (e.g., IgA nephropathy), Multiple Sclerosis, Neuritis, Uveitis Ophthalmia, Polyendoerinopathies, Purpura (e.g., Henloch-Scoenlein purpura), Reiter's Disease, Stiff-Man Syndrome, Autoimmune Pulmonary Inflammation, myocarditis, IgA glomerulonephritis, dense deposit disease, rheumatic heart disease, Guillain-Barre Syndrome, insulin dependent diabetes mellitis, and autoimmune inflammatory eye disease.

[0420] Additional autoimmune disorders and conditions associated with these disorders that may be treated, prevented, ameliorated, diagnosed and/or prognosed with the therapeutic and pharmaceutical compositions of the invention include, but are not limited to, autoimmune thyroiditis, hypothyroidism (i.e., Hashimoto's thyroiditis) (often characterized, e.g., by cell-mediated and humoral thyroid eytotoxieity), systemic lupus erhythematosus (often characterized, e.g., by circulating and locally generated immune complexes), discoid lupus, Goodpasture's syndrome (often characterized, e.g., by anti-basement membrane antibodies), Pemphigus (often characterized, e.g., by epidermal acantholytic antibodies), Receptor autoimmunities such as, for example, (a) Graves' Disease (often characterized, e.g., by TSH receptor antibodies), (b) Myasthenia Gravis (often characterized, e.g., by acetylcholine receptor antibodies), and (c) insulin resistance

(often characterized, e.g., by insulin receptor antibodies), autoimmune hemolytic anemia (often characterized, e.g., by phagocytosis of antibody-sensitized RBCs), autoimmune thrombocytopenic purpura (often characterized, e.g., by phagocytosis of antibody-sensitized platelets.

[0421] Additional autoimmune disorders and conditions associated with these disorders that may be treated, prevented, ameliorated, diagnosed and/or prognosed with the therapeutic and pharmaceutical compositions of the invention include, but are not limited to, rheumatoid arthritis (often characterized, e.g., by immune complexes in joints), schleroderma with anti-collagen antibodies (often characterized, e.g., by nucleolar and other nuclear antibodies), mixed connective tissue disease (often characterized, e.g., by antibodies to extractable nuclear antigens (e.g., ribonucleoprotein)), polymyositis/dermatomyositis (often characterized, e.g., by nonhistone ANA), pernicious anemia (often characterized, e.g., by antiparietal cell, microsomes, and intrinsic factor antibodies), idiopathic Addison's disease (often characterized, e.g., by humoral and cell-mediated adrenal cytotoxicity, infertility (often characterized, e.g., by antispermatozoal antibodies), glomerulonephritis (often characterized, e.g., by glomerular basement membrane antibodies or immune complexes) such as primary glomerulonephritis and IgA nephropathy, bullous pemphigoid (often characterized, e.g., by IgG and complement in basement membrane), Sjögren's syndrome (often characterized, e.g., by multiple tissue antibodies, and/or a specific nonhistone ANA (SS-B)), diabetes millitus (often characterized, e.g., by cell-mediated and humoral islet cell antibodies), and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis) (often characterized, e.g., by beta-adrenergic receptor antibodies), chronic active hepatitis (often characterized, e.g., by smooth muscle antibodies), primary biliary cirrhosis (often characterized, e.g., by mitchondrial antibodies), other endocrine gland failure (often characterized, e.g., by specific tissue antibodies in some cases), vitiligo (often characterized, e.g., by melanocyte antibodies), vasculitis (often characterized, e.g., by Ig and complement in vessel walls and/or low serum complement), post-MI (often characterized, e.g., by myocardial antibodies), cardiotomy syndrome (often characterized, e.g., by myocardial antibodies), urticaria (often characterized, e.g., by IgG and IgM antibodies to IgE), atopic dermatitis (often characterized, e.g., by IgG and IgM antibodies to IgE), asthma (often characterized, e.g., by IgG and IgM antibodies to IgE),

inflammatory myopathies, and many other inflammatory, granulomatous, degenerative, and atrophic disorders.

[0422] In a preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, a member of the group: autoimmune hemolytic anemia, as primary glomerulonephritis, IgA glomerulonephritis, Goodpasture's syndrome, idiopathic thrombocytopenia, Multiple Sclerosis, Myasthenia Gravis, Pemphigus, polymyositis/dermatomyositis, relapsing polychondritis, rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, Uveitis, vasculitis,and primary biliary cirrhosis.

[0423] In another preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, an immune based-rheumatologic disease, such as, for example, SLE, rheumatoid arthritis, CREST syndrome (a variant of scleroderma characterized by calcinosis, Raynaud's phenomenon, esophageal motility disorders, sclerodactyly, and telangiectasia.), Seronegative spondyloarthropathy (SpA), polymyositis/ dermatomyositis, microscopic polyangiitis, hepatitis C-associated arthritis, Takayasu's arteritis, and undifferentiated connective tissue disorder.

[0424] In a specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, rheumatoid arthritis and/or medical conditions associated therewith.

[0425] For example, an antibody, or antibodies, of the present invention are used to treat patients with clinical diagnosis of rheumatoid arthritis (RA). The patient treated preferably will not have a B cell malignancy. Moreover, the patient is optionally further treated with any one or more agents employed for treating RA such as salicylate; nonsteroidal anti-inflammatory drugs such as indomethacin, phenylbutazone, phenylacetic acid derivatives (*e.g.* ibuprofen and fenoprofen), naphthalene acetic acids (naproxen), pyrrolealkanoic acid (tometin), indoleacetic acids (sulindac), halogenated anthranilic acid (meclofenamate sodium), piroxicam, zomepirac and diflunisal; antimalarials such as chloroquine; gold salts; penicillamine; or immunosuppressive agents such as methotrexate or corticosteroids in dosages known for such drugs or reduced dosages. Preferably however, the patient is only treated with an antibody, or antibodies, of the present invention. Antibodies of the present invention are administered to the RA patient

according to a dosing schedule as described *infra*, which may be readily determined by one of ordinary skill in the art. The primary response is determined by the Paulus index (Paulus et al. Athritis Rheum. 33:477-484 (1990)), *i.e.* improvement in morning stiffness, number of painful and inflamed joints, erythrocyte sedimentation (ESR), and at least a 2-point improvement on a 5-point scale of disease severity assessed by patient and by physician. Administration of an antibody, or antibodies, of the present invention will alleviate one or more of the symptoms of RA in the patient treated as described above.

[0426] In a specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, amelioate, diagnose or prognose, lupus and/or medical conditions associated therewith. Lupus-associated conditions that may be treated, prevented, ameliorated, prognosed and/or diagnosed with the antibodies and antibody compositions of the invention include, but are not limited to, hematologic disorders (e.g., hemolytic anemia, leukopenia, lymphopenia, and thrombocytopenia), immunologic disorders (e.g., anti-DNA antibodies, and anti-Sm antibodies), rashes, photosensitivity, oral ulcers, arthritis, fever, fatigue, weight loss, serositis (e.g., pleuritus (pleurisy)), renal disorders (e.g., nephritis), neurological disorders (e.g., seizures, peripheral neuropathy, CNS related disorders), gastroinstestinal disorders, Raynaud phenomenon, and pericarditis. In a preferred embodiment, therapeutic and pharmaeeutical compositions of the invention are used to treat, prevent, ameliorate, diagnose, or prognose, renal disorders associated with systemic lupus erythematosus. In a most preferred embodiment, therapeutic and pharmaceutieal compositions of the invention are used to treat, prevent, ameliorate, diagnose, or prognose, nephritis associated with systemie lupus erythematosus. In another most preferred embodiment, therapeutie or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate lupus or glomerular nephritis.

[0427] In a further specific embodiment, antibodies of the invention are used to treat, inhibit, prognose, diagnose or prevent hemolytic anemia. For example, patients diagnosed with autoimmune hemolytic anemia (AIHA), *e.g.*, cryoglobinemia or Coombs positive anemia, are treated with an antibody, or antibodies, of the present invention. AIHA is an acquired hemolytic anemia due to auto-antibodies that react with the patient's red blood cells. The patient treated preferably will not have a B cell malignancy. Further adjunct therapies (such as glucocorticoids, prednisone, azathioprine, cyclophosphamide,

vinca-laden platelets or Danazol) may be combined with the antibody therapy, but preferably the patient is treated with an antibody, or antibodies, of the present invention as a single-agent throughout the course of therapy. Antibodies of the present invention are administered to the hemolytic anemia patient according to a dosing schedule as described *infra*, which may be readily determined by one of ordinary skill in the art. Overall response rate is determined based upon an improvement in blood counts, decreased requirement for transfusions, improved hemoglobin levels and/or a decrease in the evidenee of hemolysis as determined by standard chemical parameters. Administration of an antibody, or antibodies of the present invention will improve any one or more of the symptoms of hemolytic anemia in the patient treated as described above. For example, the patient treated as deseribed above will show an inerease in hemoglobin and an improvement in chemieal parameters of hemolysis or return to normal as measured by serum lactic dehydrogenase and/or bilirubin.

[0428] In another specific preferred embodiment, therapeutic and pharmaeeutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, Sjögren's Syndrome and/or medical conditions associated therewith.

[0429] In another specific preferred embodiment, therapeutic and pharmaeeutieal eompositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, HIV infeetion and/or medical conditions associated therewith (e.g. AIDS).

[0430] In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, Myasthenia gravis and/or medical conditions associated therewith.

[0431] In another speeific preferred embodiment, therapeutic and pharmaceutieal compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, IgA nephropathy and/or medical conditions associated therewith.

[0432] In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, hemolytic anemia and/or medical conditions associated therewith.

[0433] In another specific preferred embodiment, therapeutie and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, thyroiditis and/or medical conditions associated therewith.

[0434] In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, Goodpasture's Syndrome and/or medical conditions associated therewith.

[0435] In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, multiple sclerosis and/or medical conditions associated therewith.

[0436] In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, chronic lymphocytic leukemia (CLL) and/or medical conditions associated therewith.

[0437] In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, multiple myeloma and/or medical conditions associated therewith.

[0438] In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, Non-Hodgkin's lymphoma and/or medical conditions associated therewith.

[0439] In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, Hodgkin's disease and/or medical conditions associated therewith.

[0440] In another specific embodiment, antibodies of the invention are used to treat, inhibit, prognose, diagnose or prevent adult immune thrombocytopenic purpura. Adult immune thrombocytopenic purpura (ITP) is a relatively rare hematologic disorder that constitutes the most common of the immune-mediated cytopenias. The disease typically presents with severe thrombocytopenia that may be associated with acute hemorrhage in the presence of normal to increased megakaryocytes in the bone marrow. Most patients with ITP have an IgG antibody directed against target antigens on the outer surface of the platelet membrane, resulting in platelet sequestration in the spleen and aecelerated reticuloendothelial destruction of platelets (Bussell, J.B. Hematol. Oncol. Clin. North Am. (4):179 (1990)). A number of therapeutic interventions have been shown to be effective in the treatment of ITP. Steroids are generally considered first-line therapy, after which most patients are candidates for intravenous immunoglobulin (IVIG), splenectomy, or other medical therapies including vineristine or immunosuppressive/cytotoxic agents. Up to 80% of patients with ITP initially respond to a course of steroids, but far fewer have

complete and lasting remissions. Splenectomy has been recommended as standard second-line therapy for steroid failures, and leads to prolonged remission in nearly 60% of cases yet may result in reduced immunity to infection. Splenectomy is a major surgical procedure that may be associated with substantial morbidity (15%) and mortality (2%). IVIG has also been used as second line medical therapy, although only a small proportion of adult patients with ITP achieve remission. Therapeutic options that would interfere with the production of autoantibodies by activated B cells without the associated morbidities that occur with corticosteroids and/or splenectomy would provide an important treatment approach for a proportion of patients with ITP. Patients with clinical diagnosis of ITP are treated with an antibody, or antibodies of the present invention, optionally in combination with steroid therapy. The patient treated will not have a B cell malignancy. Antibodies of the present invention are administered to the RA patient according to a dosing schedule as described *infra*, which may be readily determined by one of ordinary skill in the art. Overall patient response rate is determined based upon a platelet count determined on two consecutive occasions two weeks apart following treatments as described above. See, George et al. "Idiopathic Thrombocytopenic Purpura: A Practice Guideline Developed by Explicit Methods for The American Society of Hematology", Blood 88:3-40 (1996), expressly incorporated herein by reference.

[0441] In another embodiment, therapeutie or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate an IgE-mediated allergic reaction or histamine-mediated allergic reaction. Examples of allergie reactions include, but are not limited to, asthma, rhinitis, eczema, chronic urticaria, and atopic dermatitis. In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent, or ameliorate anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility. In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate or modulate inflammation or an inflammatory disorder. Examples of chronic and acute inflammatory disorders that may be treated prevented or ameliorated with the therapeutic and pharmaceutical compositions of the invention include, but are not limited to, chronic prostatitis, granulomatous prostatitis and malacoplakia, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury,

endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, Crohn's disease, inflammatory bowel disease, chronic and acute inflammatory pulmonary diseases, bacterial infection, psoriasis, septicemia, cerebral malaria, arthritis, gastroenteritis, and glomerular nephritis.

[0442] In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate ischemia and arteriosclerosis. Examples of such disorders include, but are not limited to, reperfusion damage (*e.g.*, in the heart and/or brain) and cardiac hypertrophy.

[0443] Therapeutic or pharmaceutical compositions of the invention, may also be administered to modulate blood clotting and to treat or prevent blood clotting disorders, such as, for example, antibody-mediated thrombosis (i.e., antiphospholipid antibody syndrome (APS)). For example, therapeutic or pharmaceutical compositions of the invention, may inhibit the proliferation and differentiation of cells involved in producing anticardiolipin antibodies. These compositions of the invention can be used to treat, prevent, ameliorate, diagnose, and/or prognose thrombotic related events including, but not limited to, stroke (and recurrent stroke), heart attack, deep vein thrombosis, pulmonary embolism, myocardial infarction, coronary artery disease (e.g., antibody –mediated coronary artery disease), thrombosis, graft reocclusion following cardiovascular surgery (e.g., coronary arterial bypass grafts, recurrent fetal loss, and recurrent cardiovascular thromboembolic events.

[0444] Therapeutie or pharmaceutical compositions of the invention, may also be administered to treat, prevent, or ameliorate organ rejection or graft-versus-host disease (GVHD) and/or conditions associated therewith. Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. The administration of antibodies of the invention, that inhibit an immune response, may be an effective therapy in preventing organ rejection or GVHD.

[0445] In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate a disease or disorder diseases associated with increased apoptosis including, but not limited to, AIDS, neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease,

Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration), myelodysplastic syndromes (such as aplastic anemia), ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia. In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate bone marrow failure, for example, aplastic anemia and myelodysplastic syndrome.

[0446] In another embodiment, therapeutic or pharmaceutical compositions of the invention arc administercd to an animal to trcat, prevent or amcliorate growth, progression, and/or metastascs of malignancies and proliferative disorders associated with increased eell survival, or the inhibition of apoptosis. Examples of such disorders, include, but are not limited to, leukemia (*e.g.*, aeute leukemia sueh as acutc lymphocytic leukcmia and acute myelocytic leukemia), neoplasms, tumors (*e.g.*, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenie sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate canccr, squamous cell carcinoma, basal cell carcinoma, adenocareinoma, sweat gland carcinoma, scbaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung earcinoma, small cell lung carcinoma, bladder carcinoma, cpithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, and retinoblastoma), heavy chain disease, metastascs, or any disease or disorder characterized by uncontrolled ccll growth.

[0447] In a speeific embodimcnt, therapeutic or pharmaceutical compositions of the invention are used to trcat or prevent a disorder characterized by hpergammagloulinemia (e.g., AIDS, autoimmune diseases, and some immunodeficiencies).

[0448] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used to treat or prevent a disorder characterized by deficient serum immunoglobulin production, recurrent infections, and/or immune system dysfunction.

Moreover, therapeutic or pharmaceutical compositions of the invention may be used to treat or prevent infections of the joints, bones, skin, and/or parotid glands, blood-borne infections (e.g., sepsis, meningitis, septic arthritis, and/or osteomyelitis), autoimmune diseases (e.g., those disclosed herein), inflammatory disorders, and malignancies, and/or any disease or disorder or condition associated with these infections, diseases, disorders and/or malignancies) including, but not limited to, CVID, other primary immune deficiencies, HIV disease, CLL, recurrent bronchitis, sinusitis, otitis media, conjunctivitis, pneumonia, hepatitis, meningitis, herpes zoster (e.g., severe herpes zoster), and/or pneumocystis carnii.

[0449] Therapeutic or pharmaceutical compositions of the invention of the invention thereof, may be used to diagnose, prognose, treat or prevent one or more of the following diseases or disorders, or conditions associated therewith: primary immuodeficiencies, immune-mediated thrombocytopenia, Kawasaki syndrome, bone marrow transplant (e.g., recent bone marrow transplant in adults or children), chronic B-cell lymphocytic leukemia, HIV infection (e.g., adult or pediatric HIV infection), chronic inflammatory demyelinating polyneuropathy, and post-transfusion purpura.

[0450] Additionally, therapeutic or pharmaceutical eompositions of the invention may be used to diagnose, prognose, treat or prevent one or more of the following diseases, disorders, or conditions associated therewith, Guillain-Barre syndrome, anemia (e.g., anemia associated with parvovirus B19, patients with stable multiple myeloma who are at high risk for infection (e.g., recurrent infection), autoimmune hemolytic anemia (e.g., warm-type autoimmune hemolytic anemia), thrombocytopenia (e.g., neonatal thrombocytopenia), and immune-mediated neutropenia), transplantation (e.g., cytomegalovirus (CMV)-negative recipients of CMV-positive organs), hypogammaglobulinemia (e.g., hypogammaglobulinemic neonates with risk factor for infection or morbidity), epilepsy (e.g., intraetable epilepsy), systemic vasculitic syndromes, myasthenia gravis (e.g., decompensation in myasthenia gravis), dermatomyositis, and polymyositis.

[0451] Additional preferred embodiments of the invention include, but are not limited to, the use of therapeutic or pharmaceutical compositions of the invention in the following applications:

[0452] Administration to an animal (e.g., mouse, rat, rabbit, hamster, guinea pig, pigs, micro-pig, chicken, camel, goat, horse, cow, sheep, dog, cat, non-human primate, and human, most preferably human) to boost the immune system to produce increased quantities of one or more antibodies (e.g., IgG, IgA, IgM, and IgE), to induce higher affinity antibody produetion (e.g., IgG, IgA, IgM, and IgE), and/or to increase an immune response. In a specific nonexclusive embodiment, therapeutic or pharmaceutical compositions of the invention are administered to boost the immune system to produce increased quantities of IgG. In another speeific nonexclusive embodiment, antibodies of the are administered to boost the immune system to produce increased quantities of IgA. In another specific nonexclusive embodiment antibodies of the invention are administered to boost the immune system to produee inereased quantities of IgM.

[0453] Administration to an animal (including, but not limited to, those listed above, and also including transgenic animals) incapable of producing functional endogenous antibody molecules or having an otherwise compromised endogenous immune system, but which is capable of produeing human immunoglobulin molecules by means of a reconstituted or partially reconstituted immune system from another animal (see, e.g., published PCT Applieation Nos. WO98/24893, WO/9634096, WO/9633735, and WO/9110741).

[0454] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a vaccine adjuvant that enhances immune responsiveness to speeific antigen. In a specific embodiment, the vaccine is an antibody deseribed herein. In another specific embodiment, the vaccine adjuvant is a polynucleotide described herein (e.g., an antibody polynucleotide genetic vaccine adjuvant). As discussed herein, therapeutic or pharmaceutical compositions of the invention may be administered using techniques known in the art, including but not limited to, liposomal delivery, recombinant vector delivery, injection of naked DNA, and gene gun delivery.

[0455] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an adjuvant to enhance tumor-specific immune responses.

[0456] In a specific embodiment, therapeutic or pharmaceutieal compositions of the invention are used as an adjuvant to enhance anti-viral immune responses. Anti-viral immune responses that may be enhanced using the compositions of the invention as an adjuvant, include, but are not limited to, virus and virus associated diseases or symptoms

described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhanee an immune response to a virus, disease, or symptom selected from the group consisting of: AIDS, meningitis, Dengue, EBV, and hepatitis (e.g., hepatitis B). In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: HIV/AIDS, Respiratory syncytial virus, Dengue, Rotavirus, Japanese B encephalitis, Influenza A and B, Parainfluenza, Measles, Cytomegalovirus, Rabies, Junin, Chikungunya, Rift Valley fever, Herpes simplex, and yellow fever. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to the HIV gp120 antigen.

[0457] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an adjuvant to enhance anti-bacterial or anti-fungal immune responses. Anti-bacterial or anti-fungal immune responses that may be enhanced using the compositions of the invention as an adjuvant, include bacteria or fungus and bacteria or fungus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: tetanus, Diphtheria, botulism, and meningitis type B. In another speeific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group eonsisting of: Vibrio cholerae, Mycobacterium leprae, Salmonella typhi, Salmonella paratyphi, Neisseria meningitidis, Streptococcus pneumoniae, Group B streptococcus, Shigella spp., Enterotoxigenic Escheriehia coli, Enterohemorrhagic E. coli, Borrelia burgdorferi, and Plasmodium (malaria).

[0458] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an adjuvant to enhance anti-parasitic immune responses. Anti-parasitic immune responses that may be enhanced using the compositions of the invention as an adjuvant, include parasite and parasite associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a parasite. In another

specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to Plasmodium (malaria).

[0459] In a specific embodiment, compositions of the invention may be administered to patients as vaccine adjuvants. In a further specific embodiment, compositions of the invention may be administered as vaccine adjuvants to patients suffering from an immune-deficiency. In a further specific embodiment, compositions of the invention may be administered as vaccine adjuvants to patients suffering from HIV.

[0460] In a specific embodiment, compositions of the invention may be used to increase or enhance antigen-specific antibody responses to standard and experimental vaccines. In a specific embodiment, compositions of the invention may be used to enhance seroconversion in patients treated with standard and experimental vaccines. In another specific embodiment, compositions of the invention may be used to increase the repertoire of antibodies recognizing unique epitopes in response to standard and experimental vaccination.

[0461] In a preferred embodiment, antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhance antigen-specific antibody responses to standard and experimental vaccines by regulating binding of the soluble form of BLyS to a BLyS reeeptor (e.g., TACI - GenBank accession number AAC51790; BCMA - GenBank accession number NP_001183; and/or BAFF-R - GenBank accession number NP_443177). In another preferred embodiment, antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhance antigen-specific antibody responses to standard and experimental vaccines by regulating binding of the soluble form of APRIL to an APRIL receptor (e.g., BCMA and TACI).

[0462] In a preferred embodiment, antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhance seroconversion in patients treated with standard and experimental vaccines by regulating binding of the soluble form of BLyS to BLyS receptor (e.g., TACI - GenBank accession number AAC51790; BCMA - GenBank accession number NP_001183; and/or BAFF-R - GenBank accession number NP_443177). In another preferred embodiment, antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhance seroconversion in patients treated with standard and experimental

vaccines by regulating binding of the soluble form of APRIL to an APRIL receptor (e.g., BCMA and TACI).

[0463] In a preferred embodiment, antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhance the repertoire of antibodies reeognizing unique epitopes in response to standard and experimental vaccination by regulating binding of the soluble form of BLyS to a BLyS receptor (e.g., TACI - GenBank aecession number AAC51790; BCMA - GenBank accession number NP_001183; and/or BAFF-R - GenBank accession number NP_443177). In another preferred embodiment, antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhanee the repertoire of antibodies recognizing unique epitopes in response to standard and experimental vaccination by regulating binding of the soluble form of APRIL to an APRIL receptor (e.g., BCMA and TACI).

[0464] In a speeific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a stimulator of B cell responsiveness to pathogens.

[0465] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent that elevates the immune status of an individual prior to their receipt of immunosuppressive therapies.

[0466] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to induce higher affinity antibodies.

[0467] In a speeific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to increase serum immunoglobulin concentrations.

[0468] In a specific embodiment, therapeutie or pharmaceutical compositions of the invention are used as an agent to aeeelerate recovery of immunocompromised individuals.

[0469] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to boost immunoresponsiveness among aged populations.

[0470] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an immune system enhaneer prior to, during, or after bone marrow transplant and/or other transplants (e.g., allogeneic or xenogeneie organ transplantation). With respect to transplantation, compositions of the invention may be administered prior to, concomitant with, and/or after transplantation. In a specific embodiment, compositions of the invention are administered after transplantation, prior to the beginning of recovery

of T-cell populations. In another specific embodiment, compositions of the invention are first administered after transplantation after the beginning of recovery of T cell populations, but prior to full recovery of B cell populations.

[0471] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to boost immunoresponsiveness among B cell immunodeficient individuals, such as, for example, an individual who has undergone a partial or complete splenectomy. B cell immunodeficiencies that may be ameliorated or treated by administering the antibodies and/or compositions of the invention include, but are not limited to, severe combined immunodeficiency (SCID)-X linked, SCID-autosomal, adenosine deaminase deficiency (ADA deficiency), X-linked agammaglobulinemia (XLA), Bruton's disease, congenital agammaglobulinemia, X-linked infantile agammaglobulinemia, acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, transient hypogammaglobulinemia of infancy, unspecified hypogammaglobulinemia, agammaglobulinemia, common variable immunodeficiency (CVID) (acquired), Wiskott-Aldrich Syndrome (WAS), X-linked immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, selective IgA deficiency, IgG subclass deficiency (with or without IgA deficiency), antibody deficiency with normal or elevated Igs, immunodeficiency with thymoma, Ig heavy chain deletions, kappa chain deficiency, B cell lymphoproliferative disorder (BLPD), selective IgM immunodeficiency, recessive agammaglobulinemia (Swiss type), reticular dysgenesis, neonatal neutropenia, severe congenital leukopenia, thymic alymphoplasia-aplasia or dysplasia with immunodeficiency, ataxia-telangiectasia, short limbed dwarfism, X-linked lymphoproliferative syndrome (XLP), Nezelof syndrome-combined immunodeficiency with Igs, purine nucleoside phosphorylase deficiency (PNP), MHC Class II deficiency (Bare Lymphocyte Syndrome) and severe combined immunodeficiency.

[0472] In a specific embodiment, antibodies and/or compositions of the invention are administered to treat or ameliorate selective IgA deficiency.

[0473] In another specific embodiment, antibodies and/or compositions of the invention are administered to treat or ameliorate ataxia-telangiectasia.

[0474] In another specific embodiment antibodies and/or compositions of the invention are administered to treat or ameliorate common variable immunodeficiency.

[0475] In another specific embodiment, antibodies and/or compositions of the invention are administered to treat or ameliorate X-linked agammaglobulinemia.

[0476] In another specific embodiment, antibodies and/or compositions of the invention are administered to treat or ameliorate severe combined immunodeficiency (SCID).

[0477] In another specific embodiment, antibodies and/or compositions of the invention are administered to treat or ameliorate Wiskott-Aldrich syndrome.

[0478] In another specific embodiment, antibodies and/or compositions of the invention are administered to treat or ameliorate X-linked Ig deficiency with hyper IgM.

[0479] As an agent to boost immunoresponsiveness among individuals having an acquired loss of B cell function. Conditions resulting in an acquired loss of B cell function that may be ameliorated or treated by administering antibodies and/or compositions of the invention include, but are not limited to, HIV Infection, AIDS, bone marrow transplant, and B cell chronic lymphocytic leukemia (CLL).

[0480] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to boost immunoresponsiveness among individuals having a temporary immune deficiency. Conditions resulting in a temporary immune deficiency that may be ameliorated or treated by administering antibodies and/or compositions of the invention include, but are not limited to, recovery from viral infections (e.g., influenza), conditions associated with malnutrition, recovery from infectious mononucleosis, or conditions associated with stress, recovery from measles, reeovery from blood transfusion, recovery from surgery.

[0481] In a specific embodiment, therapeutic or pharmaeeutical compositions of the invention are used as a regulator of antigen presentation by monocytes, dendritic cells, T cells and/or B-cells. In one embodiment, antibody polypeptides or polynucleotides enhance antigen presentation or antagonize antigen presentation in vitro or in vivo. Moreover, in related embodiments, this enhancement or antagonization of antigen presentation may be useful in anti-tumor treatment or to modulate the immune system.

[0482] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a mediator of mucosal immune responses. The expression of BLyS on monocytes, the expression of BLyS receptor on B cells, and the responsiveness of B cells to BLyS suggests that it may be involved in exchange of signals between B cells and

monocytes or their differentiated progeny. This activity is in many ways analogous to the CD40-CD154 signalling between B cells and T cells. Anti-BLyS antibodies and compositions of the invention may therefore be good regulators of T cell independent immune responses to environmental pathogens. In particular, the unconventional B cell populations (CD5+) that are associated with mucosal sites and responsible for much of the innate immunity in humans may respond to antibodies or compositions of the invention thereby enhancing or inhibiting individual's immune status.

[0483] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to direct an individual's immune system towards development of a humoral response (i.e. TH2) as opposed to a TH1 cellular response.

[0484] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a means to induce tumor proliferation and thus make it more susceptible to anti-neoplastic agents. For example, multiple myeloma is a slowly dividing disease and is thus refractory to virtually all anti-neoplastic regimens. If these cells were forced to proliferate more rapidly, their susceptibility profile would likely change.

[0485] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a monocyte cell specific binding protein to which specific activators or inhibitors of cell growth may be attached. The result would be to focus the activity of such activators or inhibitors onto normal, diseased, or neoplastic B cell populations.

[0486] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a B cell specific binding protein to which specific activators or inhibitors of cell growth may be attached. The result would be to focus the activity of such activators or inhibitors onto normal, diseased, or neoplastic B cell populations.

[0487] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a means of detecting monocytic cells by virtue of its specificity. This application may require labeling the protein with biotin or other agents (e.g., as described herein) to afford a means of detection.

[0488] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a means of detecting B-lineage cells by virtue of its specificity. This application may require labeling the protein with biotin or other agents (e.g., as described herein) to afford a means of detection.

[0489] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a stimulator of B cell production in pathologies such as AIDS, ehronic lymphocyte disorder and/or Common Variable immunodeficieney.

[0490] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as part of a monocyte selection device the function of which is to isolate monocytes from a heterogeneous mixture of cell types. Antibodies of the invention could be coupled to a solid support to whieh monoeytes would then specifically bind. Unbound cells would be washed out and the bound cells subsequently eluted. A non-limiting use of this selection would be to allow purging of tumor cells from, for example, bone marrow or peripheral blood prior to transplant.

[0491] In a specific embodiment, therapeutie or pharmaeeutical compositions of the invention are used as part of a B cell selection device the function of which is to isolate B cells from a heterogeneous mixture of cell types. Antibodies of the invention (that do not inhibit BLyS/BLyS Receptor interaction) binding soluble BLyS could be coupled to a solid support to which B cells would then specifieally bind. Unbound cells would be washed out and the bound cells subsequently eluted. A non-limiting use of this selection would be to allow purging of tumor eells from, for example, bone marrow or peripheral blood prior to transplant.

[0492] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a therapy for generation and/or regeneration of lymphoid tissues following surgery, trauma or genetic defect.

[0493] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a gene-based therapy for genetically inherited disorders resulting in immuno-incompetence sueh as observed among SCID patients.

[0494] In a specifie embodiment, therapeutic or pharmaceutical compositions of the invention are used as an antigen for the generation of antibodies to inhibit or enhance BLyS mediated responses.

[0495] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a means of activating monocytes/macrophages to defend against parasitic diseases that effeet monocytes such as Leishmania.

[0496] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as pretreatment of bone marrow samples prior to transplant. Such treatment would increase B cell representation and thus accelerate recovery.

[0497] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a means of regulating secreted cytokines that are elicited by BLyS and/or BLyS receptor.

[0498] Antibody polypeptides or polynucleotides of the invention may be used to modulate IgE concentrations in vitro or in vivo.

[0499] Additionally, antibody polypeptides or polynucleotides of the invention may be used to treat, prevent, and/or diagnose IgE-mediated allergic reactions. Such allergic reactions include, but are not limited to, asthma, rhinitis, and eczema.

[0500] In a specific embodiment, antibody polypeptides or polynucleotides of the invention, are administered to treat, prevent, diagnose, and/or ameliorate selective IgA deficiency.

[0501] In another specific embodiment antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate ataxia-telangiectasia.

[0502] In another specific embodiment, antibody polypeptides or polynueleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate common variable immunodeficiency.

[0503] In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate X-linked agammaglobulinemia.

[0504] In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate severe combined immunodeficiency (SCID).

[0505] In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate Wiskott-Aldrich syndrome.

[0506] In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate X-linked Ig deficiency with hyper IgM. In a specific embodiment antibody polypeptides or

polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate X-linked Ig deficiency with hyper IgM.

[0507] In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, and/or diagnose chronic myelogenous leukemia, acute myelogenous leukemia, leukemia, hystiocytic leukemia, monocytic leukemia (e.g., acute monocytic leukemia), leukemic reticulosis, Shilling Type monocytic leukemia, and/or other leukemias derived from monocytes and/or monocytic cells and/or tissues.

[0508] In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate monocytic leukemoid reaction, as seen, for example, with tuberculosis.

[0509] In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate monocytic leukocytosis, monocytic leukopenia, monocytopenia, and/or monocytosis.

[0510] In a specific embodiment, antibody polypeptides or polynucleotides of the invention are used to treat, prevent, detect, and/or diagnose monocyte disorders and/or diseases, and/or conditions associated therewith.

[0511] In a specific embodiment, antibody polypeptides or polynucleotides of the invention are used to treat, prevent, detect, and/or diagnose primary B lymphocyte disorders and/or diseases, and/or conditions associated therewith. In one embodiment, such primary B lymphocyte disorders, diseases, and/or conditions are characterized by a complete or partial loss of humoral immunity. Primary B lymphocyte disorders, diseases, and/or conditions associated therewith that are characterized by a complete or partial loss of humoral immunity and that may be prevented, treated, detected and/or diagnosed with compositions of the invention include, but are not limited to, X-Linked Agammaglobulinemia (XLA), severe combined immunodeficiency disease (SCID), and selective IgA deficiency.

[0512] In a preferred embodiment antibody polypeptides or polynucleotides of the invention are used to treat, prevent, and/or diagnose diseases or disorders affecting or conditions associated with any one or more of the various mucous membranes of the body. Such diseases or disorders include, but are not limited to, for example, mucositis, mucoclasis, mucocolitis, mucocutaneous leishmaniasis (such as, for example, American

leishmaniasis, leishmaniasis americana, nasopharyngeal leishmaniasis, and New World leishmaniasis), mucocutaneous lymph node syndrome (for example, Kawasaki disease), mucoenteritis, mucoepidermoid carcinoma, mucoepidermoid tumor, mucoepithelial dysplasia, mucoid adenocarcinoma, mucoid degeneration, myxoid degeneration; myxomatous degeneration; myxomatosis, mucoid medial degeneration (for example, cystic medial necrosis), mucolipidosis (including, for example, mucolipidosis I, mucolipidosis II, mucolipidosis III, and mucolipidosis IV), mucolysis disorders, mucomembranous enteritis, mucoenteritis, mucopolysaccharidosis (such as, for example, type I mucopolysaccharidosis (i.e., Hurler's syndrome), type IS mucopolysaccharidosis (i.e., Scheie's syndrome or type V mucopolysaccharidosis), type II mucopolysaccharidosis (i.e., Hunter's syndrome), type III mucopolysaccharidosis (i.e., Sanfilippo's syndrome), type IV mucopolysaccharidosis (i.e., Morquio's syndrome), type VI mucopolysaccharidosis (i.e., Maroteaux-Lamy syndrome), type VII mucopolysaccharidosis (i.e, mucopolysaccharidosis due to beta-glucuronidase deficiency), and mucosulfatidosis), mucopolysacchariduria, mucopurulent conjunctivitis, mucopus, mucormycosis (i.e., zygomycosis), mucosal disease (i.e., bovine virus diarrhea), mucous colitis (such as, for example, mucoeolitis and myxomembranous colitis), and mueoviscidosis (such as, for example, cystic fibrosis, cystic fibrosis of the pancreas, Clarke-Hadfield syndrome, fibrocystic disease of the pancreas, mucoviscidosis, and viscidosis). In a highly preferred embodiment, antibody polypeptides or polynucleotides of the invention are used to treat, prevent, and/or diagnose mucositis, especially as associated with chemotherapy.

[0513] In a preferred embodiment, antibody polypeptides or polynucleotides of the invention are used to treat, prevent, and/or diagnose diseases or disorders affecting or conditions associated with sinusitis.

[0514] An additional condition, disease or symptom that can be treated, prevented, and/or diagnosed by antibody polypeptides or polynucleotides of the invention is osteomyelitis.

[0515] An additional condition, disease or symptom that can be treated, prevented, and/or diagnosed by antibody polypeptides or polynucleotides of the invention is endocarditis.

[0516] All of the above described applications as they may apply to veterinary medicine.

[0517] Antibody polypeptides or polynucleotides of the invention may be used to treat, prevent, and/or diagnose diseases and disorders of the pulmonary system (e.g., bronchi such as, for example, sinopulmonary and bronehial infections and conditions associated with such diseases and disorders and other respiratory diseases and disorders. In specific embodiments, such diseases and disorders include, but are not limited to, bronchial adenoma, bronchial asthma, pneumonia (such as, e.g., bronchial pneumonia, bronchopneumonia, and tuberculous bronchopneumonia), chronic obstructive pulmonary disease (COPD), bronchial polyps, bronchiectasia (such as, e.g., bronchiectasia sicca, cylindrical bronchiectasis, and saccular bronchiectasis), bronchiolar adenocarcinoma, bronchiolar carcinoma, bronchiolitis (such as, e.g., exudative bronchiolitis, bronchiolitis fibrosa obliterans, and proliferative bronchiolitis), bronchiolo-alveolar carcinoma, bronchitic asthma, bronchitis (such as, e.g., asthmatic bronchitis, Castellani's bronchitis, chronic bronchitis, croupous bronchitis, fibrinous bronchitis, hemorrhagic bronchitis, infectious avian bronchitis, obliterative bronchitis, plastic bronchitis, pseudomembranous bronchitis, putrid bronchitis, and verminous bronchitis), bronchocentric granulomatosis, bronchoedema, bronchoesophageal fistula, bronchogenic carcinoma, bronchogenic cyst, broncholithiasis, bronchomalacia, bronchomycosis (such as, e.g., bronchopulmonary aspergillosis), bronchopulmonary spirochetosis, hemorrhagic bronchitis, bronchorrhea, bronchospasm, bronchostaxis, bronchostenosis, Biot's respiration, bronchial respiration, Kussmaul respiration, Kussmaul-Kien respiration, respiratory acidosis, respiratory alkalosis, respiratory distress syndrome of the newborn, respiratory insuffieiency, respiratory scleroma, respiratory syncytial virus, and the like.

[0518] In a specific embodiment, antibody polypeptides or polynucleotides of the invention are used to treat, prevent, and/or diagnose chronic obstructive pulmonary disease (COPD).

[0519] In another embodiment, antibody polypeptides or polynucleotides of the invention are used to treat, prevent, and/or diagnose fibroses and conditions associated with fibroses, including, but not limited to, cystic fibrosis (including such fibroses as cystic fibrosis of the pancreas, Clarke-Hadfield syndrome, fibrocystic disease of the pancreas, mucoviscidosis, and viscidosis), endomyocardial fibrosis, idiopathie

retroperitoneal fibrosis, leptomeningeal fibrosis, mediastinal fibrosis, nodular subepidermal fibrosis, pericentral fibrosis, perimuscular fibrosis, pipestem fibrosis, replacement fibrosis, subadventitial fibrosis, and Symmers' clay pipestem fibrosis.

[0520] In another embodiment, therapeutic or pharmaceutical eompositions of the invention are administered to an animal to treat, prevent or ameliorate infectious diseases. Infectious diseases include diseases associated with yeast, fungal, viral and baeterial infections. Viruses causing viral infections which ean be treated or prevented in accordance with this invention include, but are not limited to, retroviruses (*e.g.*, human T-cell lymphotrophic virus (HTLV) types I and II and human immunodeficiency virus (HIV)), herpes viruses (*e.g.*, herpes simplex virus (HSV) types I and II, Epstein-Barr virus, HHV6-HHV8, and cytomegalovirus), arenavirues (*e.g.*, lassa fever virus), paramyxoviruses (*e.g.*, morbillivirus virus, human respiratory syncytial virus, mumps, and pneumovirus), adenoviruses, bunyaviruses (*e.g.*, hantavirus), cornaviruses, filoviruses (*e.g.*, Ebola virus), flaviviruses (*e.g.*, hepatitis C virus (HCV), yellow fever virus, and Japanese encephalitis virus), hepadnaviruses (*e.g.*, hepatitis B viruses (HBV)), orthomyoviruses (*e.g.*, influenza viruses A, B and C), papovaviruses (*e.g.*, papillomavirues), picornaviruses (*e.g.*, rhinoviruses, enteroviruses and hepatitis A viruses), poxviruses, reoviruses (*e.g.*, rotavirues), togaviruses (*e.g.*, rubella virus), rhabdoviruses (*e.g.*, rabies virus). Microbial pathogens causing bacterial infections include, but are not limited to, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Neisseria gonorrhoea*, *Neisseria meningitidis*, *Corynebacterium diphtheriae* , *Clostridium botulinum*, *Clostridium perfringens*, *Clostridium tetani*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Klebsiella ozaenae*, *Klebsiella rhinoscleromotis*, *Staphylococcus aureus*, *Vibrio cholerae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Campylobacter* (Vibrio) *fetus*, *Campylobacter jejuni*, *Aeromonas hydrophila*, *Bacillus cereus*, *Edwardsiella tarda*, *Yersinia enterocolitica*, *Yersinia pestis*, *Yersinia pseudotuberculosis*, *Shigella dysenteriae*, *Shigella flexneri*, *Shigella sonnei*, *Salmonella typhimurium*, *Treponema pallidum*, *Treponema pertenue*, *Treponema carateneum*, *Borrelia vincentii*, *Borrelia burgdorferi*, *Leptospira icterohemorrhagiae*, *Mycobacterium tuberculosis*, *Toxoplasma gondii*, *Pneumocystis carinii*, *Francisella tularensis*, *Brucella abortus*, *Brucella suis*, *Brucella melitensis*, *Mycoplasma spp.*, *Rickettsia prowazeki*, *Rickettsia tsutsugumushi*, *Chlamydia spp.*, and *Helicobacter pylori.*

Gene Therapy

[0521] In a specific embodiment, nucleic acids comprising sequences encoding antibodies or functional derivatives thereof, are administered to treat, inhibit or prevent a disease or disorder associated with aberrant expression and/or activity of BLyS and/or its receptor, by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect.

[0522] Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

[0523] For general reviews of the methods of gene therapy, see Goldspiel *et al.*, Clinical Pharmacy 12:488-505 (1993); Wu and Wu, Biotherapy *3:87-95* (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, TIBTECH 1 *l(5):155-215* (1993). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel *et al.* (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); and Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990).

[0524] In a preferred aspect, a composition of the invention comprises, or alternatively consists of, nucleic acids encoding an antibody, said nucleic aeids being part of an expression vector that expresses the antibody or fragments or chimeric proteins or heavy or light chains thereof in a suitable host. In particular, such nucleic acids have promoters, preferably heterologous promoters, operably linked to the antibody coding region, said promoter being inducible or constitutive, and, optionally, tissue-specific. In another particular embodiment, nucleic aeid molecules are used in which the antibody coding sequences and any other desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intrachromosomal expression of the antibody encoding nucleic aeids (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra *et al.*, Nature 342:435-438 (1989). In specific embodiments, the expressed antibody molecule is an scFv;

alternatively, the nucleic acid sequences include sequences encoding both the heavy and light chains, or fragments or variants thereof, of an antibody.

[0525] Delivery of the nucleic acids into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid- carrying vectors, or indirect, in which case, cells are first transformed with the nucleic acids in vitro, then transplanted into the patient. These two approaches are known, respectively, as *in vivo* or *ex vivo* gene therapy.

[0526] In a specific embodiment, the nucleic acid sequences are directly administered *in vivo*, where it is expressed to produce the encoded product. This can be accomplished by any of numerous methods known in the art, *e.g.*, by constructing them as part of an appropriate nucleic acid expression vector and administering it so that they become intracellular, *e.g.*, by infection using defective or attenuated retrovirals or other viral vectors (see U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle bombardment (*e.g.*, a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, encapsulation in liposomes, microparticles, or microcapsules, or by administering them in linkage to a peptide which is known to enter the nucleus, by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see, *e.g.*, Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)) (which can be used to target cell types specifically expressing the receptors), etc. In another embodiment, nucleic acid-ligand complexes can be formed in which the ligand comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted *in vivo* for cell specific uptake and expression, by targeting a specific receptor (see, *e.g.*, PCT Publications WO 92/06 180; WO 92/22635; W092/203 16; W093/14188, WO 93/20221). Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra *et al.*, Nature 342:435-438 (1989)).

[0527] In a specific embodiment, viral vectors that contains nucleic acid sequences encoding an antibody of the invention or fragments or variants thereof are used. For example, a retroviral vector can be used (see Miller *et al.*, Meth. Enzymol. 217:581-599 (1993)). These retroviral vectors contain the components neeessary for the correct packaging of the viral genome and integration into the host cell DNA. The nucleic acid

sequences encoding the antibody to be used in gene therapy are cloned into one or more vectors, which facilitates delivery of the gene into a patient. More detail about retroviral vectors can be found in Boesen *et al.*, Biotherapy 6:29 1-302 (1994), which describes the use of a retroviral vector to deliver the mdr 1 gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes *et al.*, J. Clin. Invest. 93:644-651(1994); Klein *et al.*, Blood 83:1467-1473 (1994); Salmons and Gunzberg, Human Gene Therapy 4:129-141 (1993); and Grossman and Wilson, Curr. Opin. in Genetics and Devel. 3:110-114 (1993).

[0528] Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, Current Opinion in Genetics and Development 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout *et al.*, Human Gene Therapy 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld *et al.*, Science 252:431-434 (1991); Rosenfeld *et al.*, Cell 68:143- *155* (1992); Mastrangeli *et al.*, J. Clin. Invest. 91:225-234 (1993); PCT Publication W094/12649; and Wang, *et al.*, Gene Therapy 2:775-783 (1995). In a preferred embodiment, adenovirus vectors are used.

[0529] Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh *et al.*, Proc. Soc. Exp. Biol. Med. 204:289-300 (1993); U.S. Patent No. 5,436,146).

[0530] Another approach to gene therapy involves transferring a gene to cells in tissue culture by such methods as electroporation, lipofection, calcium phosphate mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene. Those cells are then delivered to a patient.

[0531] In this embodiment, the nucleic acid is introduced into a cell prior to administration *in vivo* of the resulting recombinant cell. Such introduction can be carried

out by any method known in the art, including but not limited to transfection, electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, *e.g.*, Loeffler and Behr, Meth. Enzymol. 217:599-618 (1993); Cohen *et al.*, Meth. Enzymol. 217:618-644 (1993); Clin. Pharma. Ther. 29:69-92m (1985)) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably heritable and expressible by its cell progeny.

[0532] The resulting recombinant cells ean be delivered to a patient by various methods known in the art. Recombinant blood cells (*e.g.*, hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

[0533] Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as T lymphocytes, B lymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, *e.g.*, as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

[0534] In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

[0535] In an embodiment in which recombinant cells are used in gene therapy, nucleic acid sequences encoding an antibody or fragment thereof are introduced into the cells such that they are expressible by the cells or their progeny, and the recombinant cells are then administered in vivo for therapeutic effect. In a specifie embodiment, stem or progenitor cells are used. Any stem and/or progenitor cells which can be isolated and maintained *in vitro* can potentially be used in accordance with this embodiment of the present invention (see e.g. PCT Publication WO 94/08598; Stemple and Anderson, Cell 7 1:973-985 (1992);

Rheinwald, Meth. Cell Bio. 21A:229 (1980); and Pittelkow and Scott, Mayo Clinic Proc. 61:771 (1986)).

[0536] In a speeific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that expression of the nucleic acid is controllable by controlling the presence or absence of the appropriate inducer of transcription.

Demonstration of Therapeutic or Prophylactic Utility of a Composition

[0537] The compounds of the invention are preferably tested *in vitro*, and then *in vivo* for the desired therapeutic or prophylactic activity, prior to use in humans. For example, *in vitro* assays which can be used to determine whether administration of a specific antibody or composition of the present invention is indicated, include *in vitro* cell culture assays in which a patient tissue sample is grown in culture, and exposed to or otherwise administered an antibody or composition of the present invention, and the effect of such an antibody or composition of the present invention upon the tissue sample is observed. In various specific embodiments, *in vitro* assays can be carried out with representative cells of cell types involved in a patient's disorder, to determine if an antibody or composition of the present invention has a desired effect upon such cell types. Preferably, the antibodies or compositions of the invention are also tested in *in vitro* assays and animal model systems prior to administration to humans.

[0538] Antibodies or compositions of the present invention for use in therapy can be tested for their toxicity in suitable animal model systems, including but not limited to rats, mice, chicken, cows, monkeys, and rabbits. For *in vivo* testing of an antibody or composition's toxicity any animal model system known in the art may be used.

[0539] Efficacy in treating or preventing viral infection may be demonstrated by detecting the ability of an antibody or composition of the invention to inhibit the replication of the virus, to inhibit transmission or prevent the virus from establishing itself in its host, or to prevent, ameliorate or alleviate the symptoms of disease a progression. The treatment is eonsidered therapeutic if there is, for example, a reduction in viral load, amelioration of one or more symptoms, or a decrease in mortality and/or morbidity following administration of an antibody or composition of the invention.

[0540] Antibodies or compositions of the invention can be tested for the ability to induce the expression of cytokines such as IFN-γ, by contacting cells, preferably human cells, with an antibody or composition of the invention or a control antibody or control composition and determining the ability of the antibody or composition of the invention to induce one or more cytokines. Techniques known to those of skill in the art can be used to measure the level of expression of cytokines. For example, the level of expression of cytokines can be measured by analyzing the level of RNA of cytokines by, for example, RT-PCR and Northern blot analysis, and by analyzing the level of cytokines by, for example, immunoprecipitation followed by western blot analysis and ELISA. In a preferred embodiment, a compound of the invention is tested for its ability to induce the expression of IFN-γ.

[0541] Antibodies or compositions of the invention can be tested for their ability to modulate the biological activity of immune cells by contacting immune cells, preferably human immune cells (*e.g.*, T-cells, B-cells, and Natural Killer cells), with an antibody or composition of the invention or a control compound and determining the ability of the antibody or composition of the invention to modulate (*i.e*, increase or decrease) the biological activity of immune cells. The ability of an antibody or composition of the invention to modulate the biological activity of immune cells can be assessed by detecting the expression of antigens, detecting the proliferation of immune cells (*i.e.*, B-cell proliferation), detecting the activation of signaling molecules, detecting the effector function of immune cells, or detecting the differentiation of immune cells. Techniques known to those of skill in the art can be used for measuring these activities. For example, cellular proliferation can be assayed by ^{3}H-thymidine incorporation assays and trypan blue cell counts. Antigen expression can be assayed, for example, by immunoassays including, but not limited to, competitive and non-competitive assay systems using techniques such as western blots, immunohistochemistry radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays and FACS analysis. The activation of signaling molecules can be assayed, for example, by kinase assays and electrophoretic shift assays (EMSAs). In a preferred embodiment, the ability of an antibody or composition of the

invention to induce B-cell proliferation is measured. In another preferred embodiment, the ability of an antibody or composition of the invention to modulate immunoglobulin expression is measured.

[0542] Antibodies or compositions of the invention can be tested for their ability to reduce tumor formation in *in vitro, ex vivo* and *in vivo* assays. Antibodies or compositions of the invention can also be tested for their ability to inhibit viral replication or reduce viral load in *in vitro* and *in vivo* assays. Antibodies or compositions of the invention can also be tested for their ability to reduce bacterial numbers in *in vitro* and *in vivo* assays known to those of skill in the art. Antibodies or compositions of the invention can also be tested for their ability to alleviate of one or more symptoms associated with cancer, an immune disorder (*e.g.*, an inflammatory disease), a neurological disorder or an infectious disease. Antibodies or compositions of the invention can also be tested for their ability to decrease the time course of the infectious disease. Further, antibodies or compositions of the invention can be tested for their ability to increase the survival period of animals suffering from disease or disorder, including cancer, an immune disorder or an infectious disease. Techniques known to those of skill in the art can be used to analyze the function of the antibodies or compositions of the invention *in vivo*.

Therapeutic/Prophylactic Compositions and Administration

[0543] The invention provides methods of treatment, inhibition and prophylaxis by administration to a subject of an effective amount of antibody (or fragment or variant thereof) or pharmaceutical composition of the invention, preferably an antibody of the invention. In a preferred aspect, an antibody or fragment or variant thereof is substantially purified (*i.e.*, substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to, animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably a human.

[0544] Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin as described above; additional appropriate formulations and routes of administration can be selected from among those described herein below.

[0545] Various delivery systems are known and can be used to administer antibody or fragment or variant thereof of the invention, *e.g.*, encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the antibody or antibody fragment, receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral mucosa, rectal and intestinal mucosa, ete.) and may be administered together with other biologically aetive agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration ean also be employed, *e.g.*, by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

[0546] In a preferred embodiment the antibody of the invention is formulated in 10 mM sodium citrate, 1.9% glycine, 0.5% sucrose, 0.01% polysorbate 80, pH 6.5 (± 0.3). In another preferred embodiment, the antibody of the invention is formulated in 10 mM sodium citrate, 1.9% glycine, 0.5% sucrose, 0.01% polysorbate 80, pH 6.5 (± 0.3) for intravenous administration.

[0547] In a specific embodiment, it may be desirable to administer the pharmaceutical compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, *e.g.*, in conjunction with a wound dressing after surgery, by injeetion, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a protein, including an antibody, of the invention, care must be taken to use materials to whieh the protein does not absorb.

[0548] In another embodiment, the composition can be delivered in a vesicle, in particular a liposome (see Langer, Science 249:1527-1533 (1990); Treat *et al.*, in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353- 365 (1989); Lopez-Berestein, ibid., pp. 3 17-327; see generally ibid.).

[0549] In yet another embodiment, the composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, supra; Sefton, CRC Crit. Ref. Biomed. Eng. 14:20 1 (1987); Buchwald *et al.*, Surgery 88:507 (1980); Saudek *et al.*, N. Engl. J. Med. 321:574 (1989)). In another embodiment, polymeric materials can be used (see Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J., Macromol. Sci. Rev. Macromol. Chem. 23:61 (1983); see also Levy *et al.*, Science 228:190 (1985); During *et al.*, Ann. Neurol. 25:35 1 (1989); Howard *et al.*, J.Neurosurg. 7 1:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, *i.e.*, the brain, thus requiring only a fraction of the systemic dose (see, *e.g.*, Goodson, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138 (1984)).

[0550] Other controlled release systems are discussed in the review by Langer (Science 249:1527-1533 (1990)).

[0551] In a specific embodiment where the composition of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered *in vivo* to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, *e.g.*, by use of a retroviral veetor (see U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox- like peptide which is known to enter the nucleus (see e.g., Joliot *et al.*, Proc. Natl. Acad. Sci. USA 88:1864-1868 (1991)), etc. Alternatively, a nucleic acid can be introdueed intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

[0552] The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of an antibody or a fragment thereof, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical exeipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glyeerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers sueh as triglycerides. Oral formulation can include standard carriers such as pharmaceutieal grades of mannitol, laetose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the antibody or fragment thereof, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

[0553] In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocamne to ease pain at

the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[0554] The compositions of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartarie acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

[0555] The amount of the composition of the invention which will be effective in the treatment, inhibition and prevention of a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention can be determined by standard clinical techniques. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

[0556] For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. In preferred embodiments, a dose of 1, 4, 10, or 20 mg/kg is administered intravenously to a patient. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of therapeutic or pharmaceutical compositions of the invention may be

reduced by enhancing uptake and tissue penetration (*e.g.*, into the brain) of the antibodies by modifications such as, for example, lipidation.

[0557] The antibodies and antibody compositions of the invention may be administered alone or in combination with other adjuvants. Adjuvants that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, alum, alum plus deoxycholate (ImmunoAg), MTP-PE (Biocine Corp.), QS21 (Genentech, Inc.), BCG, and MPL. In a specific embodiment, antibody and antibody compositions of the invention are administered in combination with alum. In another specific embodiment, antibody and antibody compositions of the invention are administered in combination with QS-21. Further adjuvants that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, Monophosphoryl lipid immunomodulator, AdjuVax 100a, QS-21, QS-18, CRL1005, Aluminum salts, MF-59, and Virosomal adjuvant technology. Vaccines that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, vaccines directed toward protection against MMR (measles, mumps, rubella), polio, varicella, tetanus/diptheria, hepatitis A, hepatitis B, haemophilus influenzae B, whooping cough, pneumonia, influenza, Lyme's Disease, rotavirus, cholera, yellow fever, Japanese encephalitis, poliomyelitis, rabies, typhoid fever, and pertussis, and/or PNEUMOVAX-23™. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

[0558] In another specific embodiment, antibody and antibody compositions of the invention are used in combination with PNEUMOVAX-23™ to treat, prevent, and/or diagnose infection and/or any disease, disorder, and/or condition associated therewith. In one embodiment, antibody and antibody compositions of the invention are used in combination with PNEUMOVAX-23™ to treat, prevent, and/or diagnose any Gram positive bacterial infection and/or any disease, disorder, and/or condition associated therewith. In another embodiment, antibody and antibody compositions of the invention

are used in combination with PNEUMOVAX-23™ to treat, prevent, and/or diagnose infection and/or any disease, disorder, and/or condition associated with one or more members of the genus *Enterococcus* and/or the genus *Streptococcus*. In another embodiment, antibody and antibody compositions of the invention are used in any combination with PNEUMOVAX-23™ to treat, prevent, and/or diagnose infection and/or any disease, disorder, and/or condition associated with one or more members of the Group B streptococci. In another embodiment, antibody and antibody compositions of the invention are used in combination with PNEUMOVAX-23™ to treat, prevent, and/or diagnose infection and/or any disease, disorder, and/or condition associated with *Streptococcus pneumoniae*.

[0559] The antibody and antibody compositions of the invention may be administered alone or in combination with other therapeutic agents, including but not limited to, chemotherapeutic agents, antibiotics, antivirals, steroidal and non-steroidal anti-inflammatories, conventional immunotherapeutic agents and cytokines. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

[0560] In one embodiment, the antibody and antibody compositions of the invention are administered in combination with other members of the TNF family. TNF, TNF-related or TNF-like molecules that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, soluble forms of TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), TRAIL, AIM-II (International Publication No. WO 97/34911), APRIL (J. Exp. Med. 188(6):1185-1190 (1998)), endokine-alpha (International Publication No. WO 98/07880), Neutrokine-alpha (Internatioanl Application Publication No. WO 98/18921), OPG, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-IBB, TR2

(International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TR6 (International Publication No. WO 98/30694), TR7 (International Publication No. WO 98/41629), TRANK, TR9 (International Publication No. WO 98/56892), 312C2 (International Publication No. WO 98/06842), and TR12, and soluble forms CD154, CD70, and CD153.

[0561] In a preferred embodiment, the antibody and antibody compositions of the invention are administered in combination with CD40 ligand (CD40L), a soluble form of CD40L (e.g., AVREND™), biologically active fragments, variants, or derivatives of CD40L, anti-CD40L antibodies (e.g., agonistic or antagonistic antibodies), and/or anti-CD40 antibodies (e.g., agonistic or antagonistic antibodies).

[0562] In an additional embodiment, the antibody and antibody compositions of the invention are administered alone or in combination with an anti-angiogenic agent(s). Anti-angiogenic agents that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, Angiostatin (Entremed, Rockville, MD), Troponin-1 (Boston Life Scienees, Boston, MA), anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel (Taxol), Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, VEGI, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

[0563] Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

[0564] Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

[0565] Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide

complexes. Suitable tungstate complexes inelude ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

[0566] A wide variety of other anti-angiogenic faetors may also be utilized within the context of the present invention. Representative examples include, but are not limited to, platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, 1991); Sulphated Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326, 1992); Chymostatin (Tomkinson et al., Biochem J. 286:475-480, 1992); Cyclodextrin Tetradecasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, 1990); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, 1987); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, 1987); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-earboxyphenyl-4- chloroanthronilic acid disodium or "CCA"; (Takeuchi et al., Agents Actions 36:312-316, 1992); and metalloproteinase inhibitors such as BB94.

[0567] Additional anti-angiogenic factors that may also be utilized within the context of the present invention include Thalidomide, (Celgene, Warren, NJ); Angiostatic steroid; AGM-1470 (H. Brem and J. Folkman *J Pediatr. Surg.* 28:445-51 (1993)); an integrin alpha v beta 3 antagonist (C. Storgard et al., *J Clin. Invest.* 103:47-54 (1999));

carboxynaminolmidazole; Carboxyamidotriazole (CAI) (National Cancer Institute, Bethesda, MD); Conbretastatin A-4 (CA4P) (OXiGENE, Boston, MA); Squalamine (Magainin Pharmaceuticals, Plymouth Meeting, PA); TNP-470, (Tap Pharmaceuticals, Deerfield, IL); ZD-0101 AstraZeneca (London, UK); APRA (CT2584); Benefin, Byrostatin-1 (SC339555); CGP-41251 (PKC 412); CM101; Dexrazoxane (ICRF187); DMXAA; Endostatin; Flavopridiol; Genestein; GTE; ImmTher; Iressa (ZD1839); Octreotide (Somatostatin); Panretin; Penacillamine; Photopoint; PI-88; Prinomastat (AG-3340) Purlytin; Suradista (FCE26644); Tamoxifen (Nolvadex); Tazarotene; Tetrathiomolybdate; Xeloda (Capecitabine); and 5-Fluorouracil.

[0568] Anti-angiogenic agents that may be administered in combination with the compounds of the invention may work through a variety of mechanisms including, but not limited to, inhibiting proteolysis of the extracellular matrix, blocking the function of endothelial cell-extraeellular matrix adhesion molecules, by antagonizing the function of angiogenesis indueers such as growth factors, and inhibiting integrin receptors expressed on proliferating endothelial cells. Examples of anti-angiogenic inhibitors that interfere with extracellular matrix proteolysis and which may be administered in combination with the antibody and antibody compositions of the invention include, but are not limited to, AG-3340 (Agouron, La Jolla, CA), BAY-12-9566 (Bayer, West Haven , CT), BMS-275291 (Bristol Myers Squibb, Princeton, NJ), CGS-27032A (Novartis, East Hanover, NJ), Marimastat (British Biotech, Oxford, UK), and Metastat (Aeterna, St-Foy, Quebec). Examples of anti-angiogenic inhibitors that act by blocking the function of endothelial cell-extracellular matrix adhesion molecules and which may be administered in combination with the antibody and antibody compositions of the invention include, but are not limited to, EMD-121974 (Merek KcgaA Darmstadt, Germany) and Vitaxin (Ixsys, La Jolla, CA/Medimmune, Gaithersburg, MD). Examples of anti-angiogenic agents that act by directly antagonizing or inhibiting angiogenesis inducers and which may be administered in combination with the antibody and antibody compositions of the invention include, but are not limited to, Angiozyme (Ribozyme, Boulder, CO), Anti-VEGF antibody (Genentech, S. San Francisco, CA), PTK-787/ZK-225846 (Novartis, Basel, Switzerland), SU-101 (Sugen, S. San Francisco, CA), SU-5416 (Sugen/ Pharmacia Upjohn, Bridgewater, NJ), and SU-6668 (Sugen). Other anti-angiogenic agents act to indirectly inhibit angiogenesis. Examples of indirect inhibitors of angiogenesis which

may be administered in combination with the antibody and antibody compositions of the invention include, but are not limited to, IM-862 (Cytran, Kirkland, WA), Interferon-alpha, IL-12 (Roche, Nutley, NJ), and Pentosan polysulfate (Georgetown University, Washington, DC).

[0569] In particular embodiments, the use of antibody and antibody compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of an autoimmune disease, such as for example, an autoimmune disease described herein.

[0570] In a partieular embodiment, the use of antibody and antibody compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of arthritis. In a more partieular embodiment, the use of antibody and antibody compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of rheumatoid arthritis.

[0571] In another embodiment, antibody and antibody compositions of the invention are administered in eombination with an anticoagulant. Anticoagulants that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, heparin, warfarin, and aspirin. In a specific embodiment, antibody and antibody compositions of the invention are administered in combination with heparin and/or warfarin. In another specific embodiment, antibody and antibody compositions of the invention are administered in combination with warfarin. In another specific embodiment, antibody and antibody compositions of the invention are administered in combination with warfarin and aspirin. In another specific embodiment, antibody and antibody compositions of the invention are administered in combination with heparin. In another specific embodiment, antibody and antibody eompositions of the invention are administered in combination with heparin and aspirin.

[0572] In another embodiment, antibody and antibody compositions of the invention are administered in combination with an agent that suppresses the production of anticardiolipin antibodies. In specific embodiments, the polynucleotides of the invention are administered in combination with an agent that blocks and/or reduces the ability of anticardiolipin antibodies to bind phospholipid-binding plasma protein beta 2-glycoprotein I (b2GPI).

[0573] In certain embodiments, antibody and antibody compositions of the invention are administered in combination with antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors. Nucleoside reverse transcriptase inhibitors that may be administered in combination with the antibody and antibody compositions of the invention, include, but are not limited to, RETROVIR™ (zidovudine/AZT), VIDEX™ (didanosine/ddI), HIVID™ (zalcitabine/ddC), ZERIT™ (stavudine/d4T), EPIVIR™ (lamivudine/3TC), and COMBIVIR™ (zidovudine/lamivudine). Non-nucleoside reverse transcriptase inhibitors that may be administered in eombination with the antibody and antibody compositions of the invention, include, but are not limited to, VIRAMUNE™ (nevirapine), RESCRIPTOR™ (delavirdine), and SUSTIVA™ (efavirenz). Protease inhibitors that may be administered in combination with the antibody and antibody compositions of the invention, include, but are not limited to, CRIXIVAN™ (indinavir), NORVIR™ (ritonavir), INVIRASE™ (saquinavir), and VIRACEPT™ (nelfinavir). In a specific embodiment, antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors may be used in any combination with antibody and antibody eompositions of the invention to treat, prevent, and/or diagnose AIDS and/or to treat, prevent, and/or diagnose HIV infection.

[0574] In other embodiments, antibody and antibody compositions of the invention may be administered in combination with anti-opportunistic infection agents. Anti-opportunistic agents that may be administered in combination with the antibody and antibody compositions of the invention, include, but are not limited to, TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, ATOVAQUONE™, ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, ETHAMBUTOL™, RIFABUTIN™, CLARITHROMYCIN™, AZITHROMYCIN™, GANCICLOVIR™, FOSCARNET™, CIDOFOVIR™, FLUCONAZOLE™, ITRACONAZOLE™, KETOCONAZOLE™, ACYCLOVIR™, FAMCICOLVIR™, PYRIMETHAMINE™, LEUCOVORIN™, NEUPOGEN™ (filgrastim/G-CSF), and LEUKINE™ (sargramostim/GM-CSF). In a specific embodiment, antibody and antibody compositions of the invention are used in any eombination with TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, and/or

ATOVAQUONE™ to prophylactically treat, prevent, and/or diagnose an opportunistic *Pneumocystis carinii* pneumonia infection. In another specific embodiment, antibody and antibody compositions of the invention are used in any combination with ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, and/or ETHAMBUTOL™ to prophylactically treat, prevent, and/or diagnose an opportunistic *Mycobacterium avium* complex infection. In another specific embodiment, antibody and antibody compositions of the invention are used in any combination with RIFABUTIN™, CLARITHROMYCIN™, and/or AZITHROMYCIN™ to prophylactically treat, prevent, and/or diagnose an opportunistic *Mycobacterium tuberculosis* infection. In another specific embodiment, antibody and antibody compositions of the invention are used in any combination with GANCICLOVIR™, FOSCARNET™, and/or CIDOFOVIR™ to prophylactically treat, prevent, and/or diagnose an opportunistic cytomegalovirus infection. In another specific embodiment, antibody and antibody compositions of the invention are used in any combination with FLUCONAZOLE™, ITRACONAZOLE™, and/or KETOCONAZOLE™ to prophylactically treat, prevent, and/or diagnose an opportunistic fungal infection. In another specific embodiment, antibody and antibody compositions of the invention are used in any combination with ACYCLOVIR™ and/or FAMCICOLVIR™ to prophylactically treat, prevent, and/or diagnose an opportunistic herpes simplex virus type I and/or type II infection. In another specific embodiment, antibody and antibody compositions of the invention are used in any combination with PYRIMETHAMINE™ and/or LEUCOVORIN™ to prophylactically treat, prevent, and/or diagnose an opportunistic *Toxoplasma gondii* infection. In another specific embodiment, antibody and antibody compositions of the invention are used in any combination with LEUCOVORIN™ and/or NEUPOGEN™ to prophylactically treat, prevent, and/or diagnose an opportunistic bacterial infection.

[0575] In a further embodiment, the antibody and antibody compositions of the invention are administered in combination with an antiviral agent. Antiviral agents that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, acyclovir, ribavirin, amantadine, and remantidine.

[0576] In a further embodiment, the antibody and antibody compositions of the invention are administered in combination with an antibiotic agent. Antibiotic agents that

may be administered with the antibody and antibody compositions of the invention include, but are not limited to, amoxicillin, aminoglycosides, beta-lactam (glycopeptide), beta-lactamases, Clindamycin, chloramphenicol, cephalosporins, ciprofloxacin, ciprofloxacin, erythromycin, fluoroquinolones, macrolides, metronidazole, penicillins, quinolones, rifampin, streptomycin, sulfonamide, tetracyclines, trimethoprim, trimethoprim-sulfamthoxazole, and vancomycin.

[0577] Conventional nonspecific immunosuppressive agents, that may be administered in combination with the antibody and antibody compositions of the invention include, but are not limited to, steroids, cyclosporine, cyclosporine analogs cyclophosphamide, cyclophosphamide IV, methylprednisolone, prednisolone, azathioprine, FK-506, 15-deoxyspergualin, and other immunosuppressive agents that act by suppressing the function of responding T cells.

[0578] In specific embodiments, antibody and antibody compositions of the invention are administered in combination with immunosuppressants. Immunosuppressants preparations that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, ORTHOCLONE™ (OKT3), SANDIMMUNE™/NEORAL™/SANGDYA™ (cyclosporin), PROGRAF™ (tacrolimus), CELLCEPT™ (mycophenolate), Azathioprine, glucorticosteroids, and RAPAMUNE™ (sirolimus). In a specific embodiment, immunosuppressants may be used to prevent rejection of organ or bone marrow transplantation.

[0579] In a preferred embodiment, the antibody and antibody compositions of the invention are administered in combination with steroid therapy. Steroids that may be administered in combination with the antibody and antibody compositions of the invention, include, but are not limited to, oral corticosteroids, prednisone, and methylprednisolone (e.g., IV methylprednisolone). In a specific embodiment, antibody and antibody compositions of the invention are administered in combination with prednisone. In a further specific embodiment, the antibody and antibody compositions of the invention are administered in combination with prednisone and an immunosuppressive agent. Immunosuppressive agents that may be administered with the antibody and antibody compositions of the invention and prednisone are those described herein, and include, but are not limited to, azathioprine, cylophosphamide, and cyclophosphamide IV. In a another specific embodiment, antibody and antibody compositions of the invention

are administered in combination with methylprednisolone. In a further specific embodiment, the antibody and antibody compositions of the invention are administered in combination with methylprednisolone and an immunosuppressive agent. Immunosuppressive agents that may be administered with the antibody and antibody compositions of the invention and methylprednisolone are those described herein, and include, but are not limited to, azathioprine, cylophosphamide, and cyclophosphamide IV.

[0580] In a preferred embodiment, the antibody and antibody compositions of the invention are administered in combination with an antimalarial. Antimalarials that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, hydroxychloroquine, chloroquine, and/or quinacrine.

[0581] In a preferred embodiment, the antibody and antibody compositions of the invention are administered in combination with an NSAID.

[0582] In a nonexclusive embodiment, the antibody and antibody compositions of the invention are administered in combination with one, two, three, four, five, ten, or more of the following drugs: NRD-101 (Hoechst Marion Roussel), diclofenac (Dimethaid), oxaprozin potassium (Monsanto), mecasermin (Chiron), T-614 (Toyama), pemetrexed disodium (Eli Lilly), atreleuton (Abbott), valdecoxib (Monsanto), eltenac (Byk Gulden), campath, AGM-1470 (Takeda), CDP-571 (Celltech Chiroscience), CM-101 (CarboMed), ML-3000 (Merckle), CB-2431 (KS Biomedix), CBF-BS2 (KS Biomedix), IL-1Ra gene therapy (Valentis), JTE-522 (Japan Tobacco), paclitaxel (Angiotech), DW-166HC (Dong Wha), darbufelone mesylate (Warner-Lambert), soluble TNF receptor 1 (synergen; Amgen), IPR-6001 (Institute for Pharmaceutical Research), trocade (Hoffman-La Roche), EF-5 (Scotia Pharmaceuticals), BIIL-284 (Boehringer Ingelheim), BIIF-1149 (Boehringer Ingelheim), LeukoVax (Inflammatics), MK-663 (Merck), ST-1482 (Sigma-Tau), and butixocort propionate (WarnerLambert).

[0583] In a preferred embodiment, the antibody and antibody compositions of the invention are administered in combination with one, two, three, four, five or more of the following drugs: methotrexate, sulfasalazine, sodium aurothiomalate, auranofin, cyclosporine, penicillamine, azathioprine, an antimalarial drug (e.g., as described herein), cyclophosphamide, chlorambucil, gold, ENBREL™ (Etanercept), anti-TNF antibody, LJP 394 (La Jolla Pharmaceutical Company, San Diego, California) and prednisolone.

[0584] In a more preferred embodiment, the antibody and antibody compositions of the invention are administered in combination with an antimalarial, methotrexate, anti-TNF antibody, ENBREL™ and/or suflasalazine. In one embodiment, the antibody and antibody compositions of the invention are administered in combination with methotrexate. In another embodiment, the antibody and antibody compositions of the invention are administered in combination with anti-TNF antibody. In another embodiment, the antibody and antibody compositions of the invention are administered in combination with methotrexate and anti-TNF antibody. In another embodiment, the antibody and antibody compositions of the invention are administered in combination with suflasalazine. In another specific embodiment, the antibody and antibody compositions of the invention are administered in combination with methotrexate, anti-TNF antibody, and suflasalazine. In another embodiment, the antibody and antibody compositions of the invention are administered in combination ENBREL™. In another embodiment, the antibody and antibody compositions of the invention are administered in combination with ENBREL™ and methotrexate. In another embodiment, the antibody and antibody compositions of the invention are administered in combination with ENBREL™, methotrexate and suflasalazine. In another embodiment, the antibody and antibody compositions of the invention are administered in combination with ENBREL™, methotrexate and suflasalazine. In other embodiments, one or more antimalarials is combined with one of the above-recited combinations. In a specfic embodiment, the antibody and antibody compositions of the invention are administered in combination with an antimalarial (e.g., hydroxychloroquine), ENBREL™, methotrexate and suflasalazine. In another specfic embodiment, the antibody and antibody compositions of the invention are administered in combination with an antimalarial (e.g., hydroxychloroquine), sulfasalazine, anti-TNF antibody, and methotrexate.

[0585] In an additional embodiment, antibody and antibody compositions of the invention are administered alone or in combination with one or more intravenous immune globulin preparations. Intravenous immune globulin preparations that may be administered with the antibody and antibody compositions of the invention include, but not limited to, GAMMAR™, IVEEGAM™, SANDOGLOBULIN™, GAMMAGARD S/D™, and GAMIMUNE™. In a specific embodiment, antibody and antibody

compositions of the invention are administered in combination with intravenous immune globulin preparations in transplantation therapy (e.g., bone marrow transplant).

[0586] CD40 ligand (CD40L), a soluble form of CD40L (e.g., AVREND™), biologieally active fragments, variants, or derivatives of CD40L, anti-CD40L antibodies (e.g., agonistic or antagonistic antibodies), and/or anti-CD40 antibodies (e.g., agonistic or antagonistic antibodies).

[0587] In an additional embodiment, the antibody and antibody compositions of the invention are administered alone or in combination with an anti-inflammatory agent. Anti-inflammatory agents that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, glucocorticoids and the nonsteroidal anti-inflammatories, aminoarylcarboxylic acid derivatives, arylacetic acid derivatives, arylbutyric acid derivatives, arylcarboxylic acids, arylpropionic acid derivatives, pyrazoles, pyrazolones, salicylic acid derivatives, thiazinecarboxamides, e-acetamidocaproic acid, S-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, bueolome, difenpiramide, ditazol, emorfazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paranyline, perisoxal, pifoxime, proquazone, proxazole, and tenidap.

[0588] In another embodiment, compostions of the invention are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, antibiotic derivatives (e.g., doxorubicin, bleomycin, daunorubicin, and dactinomycin); antiestrogens (e.g., tamoxifen); antimetabolites (e.g., fluorouracil, 5-FU, methotrexate, floxuridine, interferon alpha-2b, glutamic acid, plicamycin, mercaptopurine, and 6-thioguanine); cytotoxic agents (e.g., earmustine, BCNU, lomustine, CCNU, cytosine arabinoside, cyclophosphamide, estramustine, hydroxyurea, procarbazine, mitomycin, busulfan, cis-platin, and vincristine sulfate); hormones (e.g., medroxyprogesterone, estramustine phosphate sodium, ethinyl estradiol, estradiol, megestrol acetate, methyltestosterone, diethylstilbestrol diphosphate, chlorotrianisene, and testolactone); nitrogen mustard derivatives (e.g., mephalen, chorambucil, mechlorethamine (nitrogen mustard) and thiotepa); steroids and combinations (e.g., bethamethasone sodium phosphate); and others (e.g., dicarbazine, asparaginase, mitotane, vincristine sulfate, vinblastine sulfate, and etoposide).

[0589] In a specific embodiment, antibody and antibody compositions of the invention are administered in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or any combination of the components of CHOP. In another embodiment, antibody and antibody compositions of the invention are administered in combination with Rituximab. In a further embodiment, antibody and antibody compositions of the invention are administered with Rituxmab and CHOP, or Rituxmab and any combination of the components of CHOP.

[0590] In an additional embodiment, the antibody and antibody compositions of the invention are administered in combination with cytokines. Cytokines that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, GM-CSF, G-CSF, IL2, IL3, IL4, IL5, IL6, IL7, IL10, IL12, IL13, IL15, anti-CD40, CD40L, IFN-alpha, IFN-beta, IFN-gamma, TNF-alpha, and TNF-beta. In preferred embodiments, antibody and antibody compositions of the invention are administered with BLyS (e.g., amino acids 134-285 of SEQ IF D NO:3228). In another embodiment, antibody and antibody compositions of the invention may be administered with any interleukin, ineluding, but not limited to, IL-1alpha, IL-1beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, IL-21, and IL-22. In preferred embodiments, the antibody and antibody compositions of the invention are administered in combination with IL4 and IL10.

[0591] In one embodiment, the antibody and antibody compositions of the invention are administered in combination with one or more chemokines. In specific embodiments, the antibody and antibody compositions of the invention are administered in combination with an α(CxC) chemokine selected from the group consisting of gamma-interferon inducible protein-10 (γIP-10), interleukin-8 (IL-8), platelet factor-4 (PF4), neutrophil activating protein (NAP-2), GRO-α, GRO-β, GRO-γ, neutrophil-activating peptide (ENA-78), granulocyte chemoattractant protein-2 (GCP-2), and stromal cell-derived factor-1 (SDF-1, or pre-B cell stimulatory factor (PBSF)); and/or a β(CC) chemokine selected from the group consisting of: RANTES (regulated on aetivation, normal T expressed and secreted), macrophage inflammatory protein-1 alpha (MIP-1α), macrophage inflammatory protein-1 beta (MIP-1β), monocyte chemotactic protein-1 (MCP-1), monocyte chemotactic protein-2 (MCP-2), monocyte chemotactic protein-3 (MCP-3), monocyte chemotactic protein-4 (MCP-4) macrophage inflammatory protein-1 gamma (MIP-1γ),

macrophage inflammatory protein-3 alpha (MIP-3α), macrophage inflammatory protein-3 beta (MIP-3β), macrophage inflammatory protein-4 (MIP-4/DC-CK-1/PARC), eotaxin, Exodus, and I-309; and/or the γ(C) chemokine, lymphotactin.

[0592] In another embodiment, the antibody and antibody compositions of the invention are administered with chemokine beta-8, chemokine beta-1, and/or macrophage inflammatory protein-4. In a preferred embodiment, the antibody and antibody compositions of the invention are administered with chemokine beta-8.

[0593] In an additional embodiment, the antibody and antibody compositions of the invention are administered in combination with an IL-4 antagonist. IL-4 antagonists that may be administered with the antibody and antibody compositions of the invention include, but are not limited to: soluble IL-4 receptor polypeptides, multimeric forms of soluble IL-4 receptor polypeptides; anti-IL-4 reeeptor antibodies that bind the IL-4 receptor without transducing the biological signal elicited by IL-4, anti-IL4 antibodies that block binding of IL-4 to one or more IL-4 receptors, and muteins of IL-4 that bind IL-4 receptors but do not transduee the biological signal elicited by IL-4. Preferably, the antibodies employed aceording to this method are monoclonal antibodies (ineluding antibody fragments, sueh as, for example, those described herein).

[0594] The invention also encompasses combining the polynucleotides and/or polypeptides of the invention (and/or agonists or antagonists thereof) with other proposed or conventional hematopoietic therapies. Thus, for example, the polynucleotides and/or polypeptides of the invention (and/or agonists or antagonists thereof) can be combined with compounds that singly exhibit erythropoietic stimulatory effects, sueh as erythropoietin, testosterone, progenitor cell stimulators, insulin-like growth factor, prostaglandins, serotonin, cyclic AMP, prolactin, and triiodothyzonine. Also eneompassed are combinations of the antibody and antibody eompositions of the invention with compounds generally used to treat aplastic anemia, such as, for example, methenolene, stanozolol, and nandrolone; to treat iron-deficiency anemia, such as, for example, iron preparations; to treat malignant anemia, such as, for example, vitamin B_{12} and/or folic acid; and to treat hemolytic anemia, such as, for example, adrenocortical steroids, e.g., corticoids. See e.g., Resegotti et al., Panminerva Medica, 23:243-248 (1981); Kurtz, FEBS Letters, 14a:105-108 (1982); McGonigle et al., Kidney Int., 25:437-

444 (1984); and Pavlovic-Kantera, Expt. Hematol., 8(supp. 8) 283-291 (1980), the contents of each of which are hereby incorporated by reference in their entireties.

[0595] Compounds that enhance the effects of or synergize with erythropoietin are also useful as adjuvants herein, and include but are not limited to, adrenergic agonists, thyroid hormones, androgens, hepatic erythropoietic factors, erythrotropins, and erythrogenins, See for e.g., Dunn, "Current Concepts in Erythropoiesis", John Wiley and Sons (Chichester, England, 1983); Kalmani, Kidney Int., 22:383-391 (1982); Shahidi, New Eng. J. Med., 289:72-80 (1973); Urabe et al., J. Exp. Med., 149:1314-1325 (1979); Billat et al., Expt. Hematol., 10:133-140 (1982); Naughton et al., Acta Haemat, 69:171-179 (1983); Cognote et al. in abstract 364, Proceedings 7th Intl. Cong. of Endocrinology (Quebec City, Quebec, July 1-7, 1984); and Rothman et al., 1982, J. Surg. Oncol., 20:105-108 (1982). Methods for stimulating hematopoiesis comprise administering a hematopoietically effective amount (i.e., an amount which effects the formation of blood cells) of a pharmaceutical composition containing polynueleotides and/or poylpeptides of the invention (and/or agonists or antagonists thereof) to a patient. The polynucleotides and/or polypeptides of the invention and/or agonists or antagonists thereof is administered to the patient by any suitable technique, including but not limited to, parenteral, sublingual, topical, intrapulmonary and intranasal, and those teehniques further discussed herein. The pharmaeeutical composition optionally contains one or more members of the group consisting of erythropoietin, testosterone, progenitor cell stimulators, insulin-like growth factor, prostaglandins, serotonin, cyclic AMP, prolactin, triiodothyzonine, methenolene, stanozolol, and nandrolone, iron preparations, vitamin B_{12}, folic acid and/or adrenocortical steroids.

[0596] In an additional embodiment, the antibody and antibody compositions of the invention are administered in combination with hematopoietic growth factors. Hematopoietic growth factors that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, LEUKINE™ (SARGRAMOSTIM™) and NEUPOGEN™ (FILGRASTIM™).

[0597] In an additional embodiment, the antibody and antibody compositions of the invention are administered in combination with fibroblast growth factors. Fibroblast growth factors that may be administered with the antibody and antibody compositions of

the invention include, but are not limited to, FGF-1, FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, and FGF-15.

[0598] Additionally, the antibody and antibody compositions of the invention may be administered alone or in combination with other therapeutic regimens, including but not limited to, radiation therapy. Such combinatorial therapy may be administered sequentially and/or concomitantly.

Kits

[0599] The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

[0600] The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody of the invention, preferably a purified antibody, in one or more containers. In an alternative embodiment, a kit comprises an antibody fragment that immunospecifically binds to BLyS. In a specific embodiment, the kits of the present invention contain a substantially isolated BLyS polypeptide as a control. Preferably, the kits of the present invention further comprise a control antibody which does not react with BLyS. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of an antibody to BLyS (*e.g.*, the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate). In specific embodiments, the kit may include a recombinantly produced or chemically synthesized BLyS. The BLyS provided in the kit may also be attached to a solid support. In a more specific embodiment the detecting means of the above-described kit includes a solid support to which BLyS is attached. Such a kit may also include a non-attached reporter-labeled anti-human antibody. In this embodiment, binding of the antibody to BLyS can be detected by binding of the said reporter-labeled antibody.

[0601] In an additional embodiment, the invention includes a diagnostie kit for use in screening serum containing antigens of the polypeptide of the invention. The diagnostie kit includes a substantially isolated antibody speeifieally immunoreactive with BLyS, and means for detecting the binding of BLyS to the antibody. In one embodiment, the antibody is attached to a solid support. In a specific embodiment, the antibody may be a monoclonal antibody. The detecting means of the kit may include a seeond, labeled monoelonal antibody. Alternatively, or in addition, the detecting means may include a labeled, eompeting antigen.

[0602] In one diagnostic configuration, test serum is reacted with a solid phase reagent having a surface-bound BLyS obtained by the methods of the present invention. After BLyS binds to a specific antibody, the unbound serum components are removed by washing, reporter-labeled anti-human antibody is added, unbound anti-human antibody is removed by washing, and a reagent is reacted with reporter-labeled anti-human antibody to bind reporter to the reagent in proportion to the amount of bound anti-BLyS antibody on the solid support. Typically, the reporter is an enzyme which is detected by incubating the solid phase in the presence of a suitable fluorometric, luminescent or colorimetrie substrate.

[0603] The solid surface reagent in the above assay is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip sticks, 96-well plate or filter material. These attachment methods generally include non-specific adsorption of the protein to the support or covalent attachment of the protein, typically through a free amine group, to a chemically reactive group on the solid support, such as an aetivated earboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunetion with biotinylated antigen(s).

[0604] Thus, the invention provides an assay system or kit for carrying out this diagnostic method. The kit generally includes a support with surface-bound recombinant BLyS, and a reporter-labeled anti-human antibody for detecting surface-bound anti-BLyS antibody.

[0605] In specific embodiments, the present invention encompasses a single chain Fv (scFv) having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

[0606] In specific embodiments, the present invention encompasses a single chain Fv (scFv) having an amino acid sequence of one of SEQ ID NOS: 1 to 46, 321 to 329, 1563 to 1595, and 1881 to 1908.

[0607] In specific embodiments, the present invention encompasses a single ehain Fv (scFv) having an amino acid sequence of one of SEQ ID NOS: 1563 to 1880.

[0608] In specific embodiments, the present invention encompasses a single chain Fv (scFv) having an amino aeid sequence of one of SEQ ID NOS: 1881 to 2128.

[0609] In specific embodiments, the present invention encompasses a single chain Fv (scFv) having an amino acid sequence of one of SEQ ID NOS: 1 to 1562.

[0610] In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLyS.

[0611] In specific embodiments, the present invention encompasses an antibody or fragment thereof eomprising a VH domain from an scFv having an amino aeid sequenee of one of SEQ ID NOS: 1 to 46, 321 to 329, 1563 to 1595, and 1881 to 1908.

[0612] In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VH domain from an seFv having an amino acid sequence of one of SEQ ID NOS: 1881 to 2128, and in which said antibody or fragment thereof immunospecifically binds to the membrane-bound form of BLyS.

[0613] In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1563 to 1880, and in which said antibody or fragment thereof immunospeeifically binds to the soluble form of BLyS.

[0614] In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLyS.

[0615] In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 46, 321 to 329, 1563 to 1595, and 1881 to 1908.

[0616] In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1881 to 2128, and in which said antibody or fragment thereof immunospecifically binds to the membrane-bound form of BLyS.

[0617] In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1563 to 1880, and in which said antibody or fragment thereof immunospecifically binds to the soluble form of BLyS.

[0618] In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLyS and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

[0619] In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLyS and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.and in which said VL and said VH domains are derived from the same scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

[0620] In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising an amino acid sequence of one of SEQ ID NOS: 2129 to 3227 wherein said antibody or fragment thereof immunospecifically binds BLyS.

[0621] In speeific embodiments, the antibody or fragment thereof of the invention is a whole immunoglobulin molecule.

[0622] In specific embodiments, the antibody or fragment thereof of the invention is a Fab fragment.

[0623] In specific embodiments, the antibody or fragment thereof of the invention is a Fv fragment.

[0624] In specific embodiments, the present invention encompasses a chimeric protein comprising the antibody or fragment thereof of the invention covalently linked to a heterologous polypeptide.

[0625] In specific embodiments, the present invention encompasses a composition comprising two or more types of antibodies or fragments or variants thereof, each of which type immunospecifically binds to BLyS, and each of which type of antibody or fragment thereof comprises a VH domain from a different scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

[0626] In specific embodiments, the present invention encompasses a composition comprising two or more types of antibodies or fragments or variants thereof, each of which type immunospecifically binds to BLyS, and each of which type of antibody or fragment thereof comprises a VL domain from a different scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

[0627] In specifie embodiments, the present invention encompasses a composition comprising two or more types of antibodies or fragments or variants thereof, each of which type immunospecifically binds to BLyS, and each of which type of antibody or fragment thereof comprises a VL domain from a different scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128 and wherein each type of antibody or fragment thereof further comprises a VH domain from a different scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

[0628] In specific embodiments, the present invention encompasses a composition comprising two or more types of antibodies or fragments or variants thereof, each of whieh type immunospeeifieally binds to BLyS, and each of which type of antibody or fragment thereof comprises a VH CDR3 having an amino acid sequence of one of SEQ ID NOS: 3129 to 3227.

[0629] In specific embodiments, the present invention encompasses a panel of two or more types of antibodies or fragments or variants thereof, each of which type immunospecifically binds to BLyS, and each of which type of antibody or fragment thereof comprises a VH domain from a different scFv having an amino acid sequence of one of SEQ ID NO: 1 to 2128.

[0630] In specific embodiments, the present invention encompasses a panel of two or more types of antibodies or fragments or variants thereof, each of which type immunospecifically binds to BLyS, and each of which type of antibody or fragment thereof comprises a VL domain from a different scFv having an amino acid sequence of one of SEQ ID NO: 1 to 2128.

[0631] In specific embodiments, the present invention encompasses a panel of two or more types of antibodies or fragments or variants thereof, each of which type immunospecifically binds to BLyS, and each of which type of antibody or fragment thereof comprises a VL domain from a different scFv having an amino acid sequence of one of SEQ ID NO: 1 to 2128 and wherein each type of antibody or fragment further comprises a VH domain from a different scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

[0632] In specific embodiments, the present invention encompasses a panel of two or more antibodies or fragments or variants thereof, each of which type immunospecifically binds to BLyS, and each of which type of antibody or fragment thereof comprises a VHCDR3 from a different scFv having an amino acid sequenee of one of SEQ ID NOS: 2129 to 3227.

[0633] In specific embodiments, the antibodies or fragments thereof of the antibody panel of the invention, are each in a well of a 96 well plate.

[0634] In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLyS.

[0635] In specific embodiments, the present invention encompasses an isolated nucleic aeid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 46, 321 to 329, 1563 to 1595, and 1881 to 1908, wherein said antibody or fragment thereof immunospecifically binds BLyS.

[0636] In specific embodiments, the present invention encompasses an isolated nueleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1881 to 1908, wherein the antibody of fragment thereof immunospecifically binds the membrane-bound form of BLyS.

[0637] In specific embodiments, the present invention encompasses an isolated nucleic acid molecule eomprising a nucleotide sequence eneoding an antibody or fragment thereof comprising a VH domain from an scFv having an amino acid sequence of one of SEQ ID

NOS: 1563 to 1569, wherein said antibody of fragment thereof immunospecifically binds the soluble form of BLyS. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule whieh is operably linked to a heterologous promoter, as well as host eells, ineluding mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-deseribed host cells under conditions in which the nucleic acid molecule is expressed.

[0638] In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequenee of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospeeifically binds BLyS. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors eomprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleie acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, eomprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host eells, comprising the above-described veetors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

[0639] In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence eneoding an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 46, 321 to 329, 1563 to 1595, and 1881 to 1908, wherein said antibody or fragment thereof immunospecifically binds BLyS. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the

antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described veetors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic aeid molecule is expressed.

[0640] In specifie embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1881 to 2128, wherein the antibody of fragment thereof immunospecifically binds the membrane-bound form of BLyS. The present invention also encompasses vectors comprising the isolated nucleic acid moleeule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nueleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid moleeule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

[0641] In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1563 to 1880, wherein said antibody of fragment thereof immunospecifically binds the soluble form of BLyS. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nueleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host eells, including mammalian host cells, comprising the above-described vectors.

Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

[0642] In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLyS and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

[0643] In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLyS and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128 and in which said VL domain and said VH domain are derived from the same scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors.

Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

[0644] In speeific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VHCDR3 from an scFv having an amino acid sequence of one of SEQ ID NOS: 2129 to 3227, wherein said antibody or fragment thereof immunospecifically binds BLyS. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, eomprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

[0645] In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to BLyS, said antibody or fragment thereof comprising an amino acid sequence of a VH domain encoded by a nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence encoding a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

[0646] In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to BLyS, said antibody or fragment thereof comprising an amino acid sequence of a VL domain encoded by a nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence encoding a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

[0647] In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifieally binds to BLyS, said antibody or fragment thereof comprising an amino acid sequence of a VH domain encoded by a nucleotide

sequence that hybridizes under highly stringent conditions to a nucleotide sequence encoding a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

[0648] In specifie embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to BLyS, said antibody or fragment thereof comprising an amino acid sequence of a VL domain encoded by a nucleotide sequence that hybridizes under highly stringent conditions to a nueleotide sequence encoding a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

[0649] In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to BLyS, said antibody or fragment thereof comprising an amino acid sequence of a CDR encoded by a nueleotide sequence that hybridizes under stringent conditions to a nueleotide sequenee encoding a CDR from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

[0650] In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to BLyS, said antibody or fragment thereof comprising an amino acid sequence of a CDR encoded by a nucleotide sequence that hybridizes under highly stringent conditions to a nucleotide sequence encoding a CDR from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

[0651] In speeific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to BLyS, said antibody or fragment thereof comprising an amino acid sequence of a VH CDR3 encoded by a nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence eneoding a VH CDR3 having an amino acid sequence of one of SEQ ID NOS: 2129 to 3227.

[0652] In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to BLyS, said antibody or fragment thereof comprising an amino aeid sequence of a VH CDR3 encoded by a nuclcotide sequence that hybridizes under highly stringent conditions to a nucleotide sequence encoding a VH CDR3 having an amino aeid sequence of one of SEQ ID NOS: 2129 to 3227.

[0653] In specific embodiments, the present invention provides a method for detecting of aberrant expression of BLyS, comprising:

[0654] assaying the level of BLyS expression in cells or a tissue sample of an individual using one or more antibodies or fragments or variants thereof that immunospecifically bind BLyS; and

[0655] comparing the level of BLyS assayed in the cells or a tissue sample with a standard level of BLyS or a level of BLyS in cells or a tissue sample from an individual without aberrant BLyS expression, wherein an increase or decrease in the assayed level of BLyS or level in cells or a tissue sample from an individual without aberrant BLyS expression compared to the standard level of BLyS is indicative of aberrant expression.

[0656] In specific embodiments, the present invention provides a method for diagnosing a disease or disorder associated with aberrant BLyS expression or aetivity, comprising:

[0657] administering to a subject an effective amount of a labeled antibody or fragment thereof that immunospecifically binds to BLyS;

[0658] waiting for a time interval following the administering for permitting the labeled antibody or fragment thereof to preferentially concentrate at sites in the subject where BLyS is expressed;

[0659] determining background level; and

[0660] detecting the labeled antibody or fragment thereof in the subject, such that detection of labeled antibody or fragment thereof above the background level indicates that the subject has a particular disease or disorder associated with aberrant expression of BLyS.

[0661] In specifie embodiments, the antibody or fragment thereof utilized in the two methods described immediately above comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

[0662] In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above comprises a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

[0663] In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above comprises a VH CDR3 having an amino acid sequence of one of SEQ ID NOS: 2129 to 3227.

[0664] In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above is conjugated to a diagnostic agent.

[0665] In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above is conjugated to a diagnostic agent wherein the diagnostic agent is horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase.

[0666] In speeific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above is conjugated to a diagnostic agent wherein the diagnostic agent is fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin.

[0667] In speeific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above is conjugated to a diagnostie agent wherein the diagnostic agent is ^{125}I, ^{131}I, ^{111}In, ^{90}Y or ^{99}Tc.

[0668] In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above is eonjugated to a diagnostic agent wherein the diagnostic agent is luciferase, luciferin or aequorin.

[0669] A pharmaceutical eomposition comprising at least one antibody or fragment thereof of comprising a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLyS and a pharmaceutically acceptable carrier.

[0670] A pharmaeeutical composition comprising at least one antibody or fragment thereof of comprising a VL domain from an scFv having an amino acid sequenee of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifieally binds BLyS and a pharmaceutieally aeeeptable carrier.

[0671] A pharmaceutieal composition comprising at least one antibody or fragment thereof of comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLyS and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128 and a pharmaceutically acceptable carrier.

[0672] A pharmaceutical composition comprising at least one antibody or fragment thereof of comprising an amino acid sequence of one of SEQ ID NOS: 2129 to 3227 wherein said antibody or fragment thereof immunospecifically binds BLyS and a pharmaceutically acceptable carrier.

[0673] A method of treating, preventing or ameliorating a disease or disorder assoeiated with aberrant BLyS expression or activity, comprising administering to an animal in need thereof the pharmaceutical composition comprising at least one antibody or fragment thereof of comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLyS and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128 and a pharmaceutically acceptable carrier in an amount effective to treat, prevent or ameliorate the disease or disorder. This method may be used to treat an infectious disorder, cancer, and/or an autoimmune disease such as lupus or glomerular nephritis.

[0674] A method of treating, preventing or ameliorating a disease or disorder associated with aberrant BLyS expression or activity, comprising administering to an animal in need thereof the pharmaceutical composition comprising at least one antibody or fragment thereof of comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLyS and a pharmaceutically acceptable carrier in an amount effective to treat, prevent or ameliorate the disease or disorder. This method may be used to treat an infectious disorder, cancer, and/or an autoimmune disease such as lupus or glomerular nephritis.

[0675] A method of treating, preventing or ameliorating a disease or disorder associated with aberrant BLyS expression or activity, comprising administering to an animal in need thereof the pharmaceutical composition comprising at least one antibody or fragment thereof of comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLyS and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128 and a pharmaceutically acceptable carrier in an amount effective to treat, prevent or ameliorate the disease or disorder. This method may be used to treat an infectious disorder, cancer, and/or an autoimmune disease such as lupus or glomerular nephritis.

[0676] A method of treating, preventing or ameliorating a disease or disorder associated with aberrant BLyS expression or activity, comprising administering to an animal in need thereof the pharmaceutical composition of comprising at least one antibody

or fragment thereof of comprising an amino acid sequence of one of SEQ ID NOS: 2129 to 3227 wherein said antibody or fragment thereof immunospecifically binds BLyS and a pharmaceutically acceptable carrier in an amount effective to treat, prevent or ameliorate the disease or disorder. This method may be used to treat an infectious disorder, cancer, and/or an autoimmune disease such as lupus or glomerular nephritis.

[0677] This method may be used to treat an infectious disorder, cancer, and/or an autoimmune disease such as lupus or glomerular nephritis.

EXAMPLES

Abbreviations

0.2 M Tris-HCl, 0.5 mM EDTA, 0.5 M sucrose (TES)
1-ethyl-3-[3-dimethylaminopropyl]carbo diimide hydrochloride (EDC)
2TY supplemented with 100μg/ml ampicillin and 2% glucose (2TYAG)
2TY supplemented with 100μg/ml ampicillin and 50μg/ml kanamycin (2TYAK)
3,3',5,5'-Tetramethyl Benzidine (TMB)
50% inhibitory concentration (IC_{50})
6xPBS containing 18% Marvel blocking solution (6xMPBS)
Absorbance (A)
Bovine serum albumin (BSA)
Enzyme linked immunosorbent assay (ELISA)
Foetal calf serum (FCS)
Heavy chain variable (V_H)
Hepes buffered saline (HBS)
Horseradish peroxidase (HRP)
Immobilised Metal Affinity Chromatography (IMAC)
Isopropyl ß-D-thiogalactopyranoside (IPTG)
Light chain variable(V_L)
Multiplicity of infection (MOI)
N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid] (Hepes)

Nanomolar (nM)
N-Hydroxysuccinimide (NHS)
PBS containing 3% Marvel (MPBS)
Phosphate Buffered Saline (PBS)
Phosphate Buffered Saline + 0.1% (v/v) Tween 20 (PBST)
Picomolar (pM)
Single chain fragment variable (scFv)
Tumour Neerosis Factor-alpha (TNF-α)
Tumour Necrosis Factor-beta (TNF-β)
TNF-related apoptosis inducing ligand (TRAIL)

Definitions:

[0678] In the following section "immobilized BLyS" refers to a soluble form of BLyS or biotinylated BLyS coated on a plastic assay plate (e.g., a 96 well plate), but does not refer to histidine tagged BLyS coated on a plastic assay plate.; "biotinylated BLyS" is a soluble form of BLyS except when used to coat an ELISA plate, in which case it would be "immobilized BLyS." Membrane bound forms of BLyS include, but are not limited to, U937 and P388 plasma membranes. Antibodies of the present invention are defined as able to bind the membrane bound and/or soluble forms of BLyS according to the assays described in Examples 1 through 19.

Example 1: Antibodies Immunospecifically Binding to Soluble And Membrane-Bound BLyS

[0679] A library of phage was screened in an assay to identify those phage displaying scFvs that immunospecifically bind to the soluble and membrane-bound forms of BLyS. Phage displaying scFvs that bound to immobilized BLyS were identified after panning on immobilized BLyS and assessment by ELISA for binding to immobilized BLyS. The BLyS that was immobilized on plates for these assays was purified from supernatants of Sf9 cells infected with a baculovirus expression construct as described in Moore et al., Science 285:260-263 which is hereby incorporated by reference in its entirety. Each of the identified scFvs were then sequenced. Certain sequences were isolated multiple times, thus a panel (panel 1) containing one member of each unique sequences was generated and

further characterized for their ability to immunospecifically bind to the soluble and membrane-bound forms of BLyS.

[0680] The derived amino acid sequences of these scFvs are shown in Table 1 above. The individual V_H and V_L segments of the scFvs were aligned to the known human germline sequences in V-BASE (Tomlinson et al, www.mrc-cpe.cam.ac.uk) and the closest germline identified.

Example 2: Specificity of scFvs for BLyS and Membrane-Bound BLyS

[0681] The specificity of each of the scFvs for both BLyS and membrane-bound BLyS was determined by phage ELISA. BLyS was immobilised onto plastic as a purified soluble form of the protein or as a membrane-bound form present on plasma membrane preparations from the human macrophage-like cell line, U937.

Maintenance of U937 Cells

[0682] U937 cells are a human monocyte-like, histiocytic lymphoma cell line known to express BLyS on their plasma membranes. They were maintained in RPMI-1640 supplemented with 4mM L-glutamine, 10% FCS, 10 U penicillin, 100 g/ml streptomycin (all reagents from Sigma). The cells were thawed from frozen stock and are either used for plasma membrane preparation, or split 1:5, after 2 days in culture when the cell density reaches 1 x 10^6/ml.

Preparation of U937 Plasma Membranes

[0683] To prepare plasma membranes, $1x10^9$ U937 cells were harvested from their culture medium by centrifugation at 1000 rpm at 4°C for 5 minutes in a benchtop centrifuge. The cells were resuspended in 40 ml 12 mM Tris, pH 7.5, 250 mM sucrose and placed on ice. The cells are then lysed using a hand-held electric homogenizer (Labortechnik IKA Ultra-Turrax) for four, one minute, bursts. To check that cell lysis had occurred, 10 μl cell lysate was added to 10 μl Trypan blue and the cell lysate was examined under a microscope. After confirming lysis, the homogenate was centrifuged at 270 x g, for 10 minutes at 4°C to pellet the nuclear fraction and the supernatant was retained. The supernatant was centrifuged at 8000 x g, 10 mins, 4°C, to pellet the mitochondrial and lysosomal fractions and the supernatant was retained. The supernatant

was then centrifuged at 100000 x g, 60 mins, 4°C to pellet the plasma membrane enriched fraction. The supernatant was discarded and the plasma membrane pellet was resuspended in 1 ml PBS and stored at -70°C. The protein concentration of the plasma membrane fraction was determined using a protein quantification kit (Biorad). Typical yields were between 5 and 10 mg of plasma membranes.

Phage ELISA

[0684] To determine the specificity of each of the unique scFvs, a phage ELISA was performed for each scFv against human BLyS, U937 plasma membranes, TNFα (R&D Systems, Minneapolis, MN), BSA and uncoated well. Individual *E. coli* colonies containing a phagemid representing one of the unique scFvs from panel 1were inoculated into 96-well plates containing 100 μl 2TYAG medium per well. Plates were incubated at 37°C for 4 hours, shaking. M13KO7 helper phage was added to each well to a MOI of 10 and the plates were incubated for a further 1 hour at 37°C. The plates were centrifuged in a benchtop centrifuge at 2000 rpm for 10 minutes. The supernatant was removed and cell pellets were resuspended in 100 μl 2TYAK and incubated at 30°C overnight, shaking. The next day, plates were centrifuged at 2000 rpm for 10 min and the 100 μl phage-containing supernatant from each well carefully transferred into a fresh 96-well plate. Twenty μl of 6xMPBS was added to each well, and incubated at room temperature for 1 hour to pre-block the phage prior to ELISA.

[0685] Flexible 96-well plates (Falcon) were coated overnight at 4°C with human BLyS (1 μg/ml) in PBS, U937 plasma membranes (10 μg/ml) in PBS, TNFα (1 μg/ml) in PBS, BSA (1 μg/ml) in PBS, or PBS. After coating, the solutions were removed from the wells, and the plates were blocked for 1 hour at room temperature in MPBS. The plates were washed 3 times with PBS and then 50 μl of pre-blocked phage was added to each well. The plates were incubated at room temperature for 1 hour and then washed with 3 changes of PBST followed by 3 changes of PBS. To each well, 50 μl of an anti-gene VIII-HRP conjugate (Pharmacia) at a 1 to 5000 dilution in MPBS was added and the plates incubated at room temperature for 1 hour. Each plate was washed three times with PBST followed by three times with PBS. Then 50 μl of an HRP-labelled anti-mouse polymer (DAKO EnVision) diluted 1/50 in 3% MPBS was added and incubated for 1 hour at room temperature. Each plate was then washed three times with PBST followed by three times

with PBS. Fifty μl of TMB substrate was then added to each well, and incubated at room temperature for 30 minutes or until colour development. The reaction was stopped by the addition of 25 μl of 0.5 M H_2SO_4. The signal generated was measured by reading the absorbance at 450nm (A_{450}) using a microtiter plate reader (Bio-Rad 3550).

[0686] The results for 3 clones (I006E07, I008D05 and I016F04) are shown in Figure 1. All 3 scFvs recognize immobilized BLyS and U937 plasma membranes but do not recognize TNFα, BSA or an uncoated well (PBS only). These results indicate that these scFvs specifically recognize immobilized BLyS and membrane-bound BLyS.

Example 3: Inhibition in an In Vitro Receptor Binding Assay by Phage ScFvs

[0687] All of the unique phage scFvs in panel 1 were assessed for their ability to inhibit soluble BLyS binding to its cognate receptor on IM9 cells.

Biotinylation of BLyS

[0688] One hundred μg of either human or mouse BLyS was dialysed overnight at 4° C against 50 mM sodium bicarbonate (sodium hydrogen carbonate) pH8.5 using a slide-a-lyzer cassette (Pierce). The next day, NHS-biotin (Pierce) was dissolved in DMSO to 13.3 mg/ml. This was then added to the BLyS at a molar ratio of 20:1 biotin:BLyS, mixed and incubated on ice for 2 hours. The biotinylated BLyS was then dialysed back into sterile PBS (Sigma) using a slide-a-lyzer cassette overnight at 4°C. The biological activity of the biotinylated BLyS was confirmed using the receptor binding inhibition assay (see below).

Maintenance of IM9 cells

[0689] IM9 cells are a human B lymphocyte cell line. They were maintained in RPMI-1640 supplemented with 4 mM L-glutamine, 10% FCS, 10 U penicillin, 100 g/ml streptomycin (all reagents from Sigma). The cells are thawed from frozen stock and can be used in assays after 5 days in culture when they reach a density of 4 - 8 x 10^5 /ml.

Receptor binding inhibition assay

[0690] Individual *E. coli* colonies containing a phagemid representing one of the unique scFvs from panel 1 were inoculated into 96-well plates containing 100 μl 2TYAG medium per well. Plates were incubated at 37° C for 4 hours, shaking. M13KO7 helper

phage was added to each well to a MOI of 10 and the plates were incubated for a further 1 hour at 37°C. The plates were centrifuged in a benchtop centrifuge at 2000 rpm for 10 minutes. The supernatant was removed and cell pellets were resuspended in 100 μl 2TYAK and incubated at 30°C overnight, shaking. The next day, plates were centrifuged at 2000 rpm for 10 min and the 100 μl phage-containing supernatant from each well carefully transferred into a fresh 96-well plate. Phage were diluted 1 in 2 in MPBS prior to use.

[0691] Flat-bottomed 96-well plates (Costar) were coated with 100 µl per well of a 1:10 dilution of poly-L-lysine (Sigma) in PBS for 1 hour at room temperature. The plates were then washed twice with water, allowed to air-dry and placed at 4° C overnight. One hundred μl of IM9 cells (at 10^6/ml in RPMI-1640 culture medium) were then added to each well. Plates were then centrifuged at 3200 rpm for 5 mins to pellet the cells. The media was earefully aspirated and 200 µl of MPBS added to each well. The plates were then allowed to block for 1 hour at room temperature.

[0692] To a separate 96-well plate 10 µl of biotinylated BLyS (at 162.5 ng/ml) in MPBS was added to each well to give a final concentration of 25 ng/ml. Fifty-five µl of each appropriate phage supernatant was added to each well and the final volume in each well was 65 µl. Plates were then incubated at room temperature for 30 minutes.

[0693] The IM9 coated plates were washed twice in PBS, tapped dry and immediately 50 µl of the phage/biotinylated-BLyS mix was added and incubated at room temperature for 1 hour. Plates were washed three times in PBST and three times in PBS, tapped dry and 50 µl of streptavidin-Delfia (Wallac) was added to each well at 1:1000 dilution in the Manufacturer's assay buffer. The plates were then incubated at room temperature for 1 hour and washed six times in Delfia wash solution (Wallac). After tapping the plates dry, 100 µl per well of Delfia enhancement solution (Wallac) was added. The plates were gently tapped to encourage micelle formation, incubated at room temperature for 10 minutes, and fluorescence read on a Wallac 1420 workstation at 6520 nM.

[0694] Results for 3 phage scFvs (I001C09, I018D07 and I016H07) that inhibited the binding of biotinylated BLyS are shown in Figure 2. Maximal binding of biotinylated BLyS to its receptor (bio-BLyS only), the background signal in the absence of biotinylated BLyS (no bio-BLyS), and results with an irrelevant (*i.e.*, does not recognize BLyS) phage antibody are also shown. All 3 phage scFvs inhibited biotinylated BLyS binding to its

receptor on IM9 cells, identifying these scFvs as scFvs that bind the soluble form of BLyS. These scFvs also bind to U937 membranes, thus they also bind the membrane bound form of BLyS.

[0695] Forty-eight of the scFvs from panel 1 that demonstrated the greatest inhibition as phage particles in this assay were chosen for further study. These 48 scFvs are listed in Table 3.

Table 3. scFvs that Inhibit the Binding of Biotinylated-BLyS to its Receptor

Antibody	Antibody	Antibody	Antibody	Antibody
I008C02	I029D07	I008C03	I008C12	I028A06
I022E02	I061E07	I007H08	I061H01	I031C03
I018C02	I006D07	I008A11	I006D08	I031F02
I008B01	I017D10	I061D02	I026E03	I031F09
I016F04	I007B03	I008A09	I027A07	I031G11
I016E05	I018C10	I007F11	I016H07	I050A07
1018H08	I001C09	I037E07	I021B05	I050A12
I018H09	I018D07	I037E12	I031G10	I050B11
	I029F11	I016F02	I031G08	I051C04
	I022D01		I031C07	I003F12
			I012A06	

Example 4: Specificity of Anti-BLyS Antibodies

[0696] The specificity of the 48 scFvs listed in Table 3 for human and murine BLyS was determined using phage ELISA.

<u>Phage ELISA</u>

[0697] To determine the specificity of the 48 scFvs, a phage ELISA was performed against human and mouse BLyS, and a panel of related and unrelated human antigens: Fas ligand, TRAIL, TNFα, TNFβ, and PBS. The : Fas ligand, TRAIL, TNFα, and TNFβ antigens were obtained from R&D Systems, Minneapolis, MN. Individual *E. coli* colonies

eontaining phagemid were inoculated into 5 ml 2YTAG and incubated at 37°C for 4 hours, shaking. M13KO7 helper phage (Pharmacia) was added to each tube to a MOI of 10 and incubated for 30 minutes at 37°C for 1 hour, the first 30 minutes static and the final 30 minutes with gentle shaking. Cells were pelleted by centrifugation at 3,500 rpm for 10 minutes and the supernatant discarded. Cell pellets werc resuspended in 5 ml 2TYAK and incubated at 30°C overnight with shaking. The next day, the cells were pelleted by eentrifugation at 3,500 rpm for 10 minutes. The phage-containing supernatant (5 ml) was carefully transferred to a fresh tube, 1 ml of 6MPBS was added, and the tube was incubated at room temperature for 1 hour to pre-block the phage prior to ELISA.

[0698] All antigens were coated at 1 μg/ml. ELISAs were performed essentially as described in Example 2. The only exception to this being the detection of phage antibody binding to mouse BLyS where the step involving incubation with the HRP-labelled anti-mouse polymer was omitted. Binding to mouse BLyS was detected with TMB as in Example 2.

[0699] All 48 scFvs are specific for immobilized human BLyS and 43 out of the 48 scFvs eross-react with immobilized mouse BLyS but not with any other unrelated or related antigen tested. I008C03, I007F11, I037E07, I037E12, and I016H07 did not bind murine BLyS. Results for two scFvs, I022D01 and I031F02, are shown in Figure 3. Both these scFvs specifically recognize human and mouse BLyS but not any other unrelated or related antigen tested.

Example 5: Specificity for the Membrane-Bound Form of BLyS

[0700] The specificity of 48 scFvs for membrane-bound BLyS was determined by the phage ELISA described in Example 2. BLyS was immobilised onto plastic as a membrane-bound form present on plasma membranes preparations from the human macrophage-like cell line, U937. This cell line is known to express the membrane-bound form of human BLyS.

[0701] To demonstrate that this binding is specific for membrane-bound BLyS, a competition ELISA was developed to determine if the ELISA signal for an individual antibody on U937's could be competed out by pre-incubation with either BLyS or TNFα. An anti-BLyS antibody that also recognizes membrane-bound BLyS would be expected to demonstrate a signal reduction with free BLyS but not free TNFα.

Competition ELISA

[0702] Individual *E. coli* colonies containing phagemid for each of the 48 scFvs listed in Table 3 were inoculated into 5 ml 2YTAG and incubated at 37°C for 4 hours, shaking. M13KO7 helper phage (Pharmacia) was added to each tube to a MOI of 10 and incubated for 30 minutes at 37° C for 1 hour, the first 30 minutes static and the final 30 minutes with gentle shaking. Cells were pelleted by centrifugation at 3,500 rpm for 10 minutes and the supernatant discarded. Cell pellets were resuspended in 5 ml 2TYAK and incubated at 30°C overnight with shaking. The next day, the cells were pelleted by centrifugation at 3,500 rpm for 10 minutes. The phage-containing supernatants (5 ml) were carefully transferred to a fresh tube.

[0703] For each of the 48 scFvs listed in Table 3, two aliquots of 20 μl 6xMPBS were pipetted into separate wells of a 96-well plate (Greiner). The first aliquot was supplemented with BLyS to a final concentration of 0.5 μg/ml. The second aliquot was supplemented with TNF-α to a final concentration of 0.5 μg/ml. Each experiment was performed in triplicate. One hundred μl of each phage supernatant was then added to each aliquot and mixed by pipetting up and down. The phage were incubated (± competing antigen) at room temperature for 1 hour.

[0704] Flexible 96-well plates (Falcon) were coated overnight at 4°C with 50 μl of 10 μg/ml U937 plasma membranes. After coating, the plates were washed 3 times with PBS and blocked for 1 hour at room temperature with 200 μl MPBS. The plates were washed 3 times with PBS and 50 μl of phage (± competing antigen) was added to each appropriate well. The plates were incubated at room temperature for 1 hour and then washed with 3 changes of PBST followed by 3 changes of PBS. To each well, 50 μl of a mouse anti-gene VIII-HRP conjugate (Pharmacia) at a 1:5000 dilution in MPBS was added and the plates incubated at room temperature for 1 hour. Each plate was washed three times with PBST followed by three times with PBS. Then 50 μl of an HRP-labelled anti-mouse polymer (DAKO EnVision) diluted 1:50 in 3% MPBS was added and incubated for 1 hour at room temperature. Each plate was then washed three times with PBST followed by three times with PBS. Fifty μl of TMB substrate was then added to each well, and incubated at room temperature for 30 to 60 minutes or until color development. The reaction was stopped by the addition of 25 μl of 0.5 M H_2SO_4. The signal generated was

measured by reading the absorbance at 450nm (A_{450}) using a microtiter plate reader (Bio-Rad 3550).

[0705] All 48 scFvs bind to U937 plasma membrane preparations. This signal could be competed out by pre-incubation of the phage antibody with BLyS but not by pre-incubation with TNF-α. This indicates that the 48 scFvs specifically recognize membrane-bound BLyS as well as soluble BLyS. Typical results are exemplified by scFvs I031F09, I050A12 and I051C04 and are shown in Figure 4. All 3 scFvs demonstrate binding to U937 plasma membranes. This binding was specifically competed out with BLyS but did not compete with TNF-α, demonstrating specific recognition of membrane-bound BLyS.

Example 6: scFv Off-rate Determinations

[0706] All off-rate determinations were performed on BIAcore 2000 machines, using the BIAcore 2000 Control Software and evaluated using the BIAevaluation 3.0 software.

Preparation of a Low Density BLyS Surfaee

[0707] A 500RU surface was prepared for kinetie studies with purified seFvs. A low density BLyS surface (500 RU BLyS coupled) was prepared in flow cell 2 by amine coupling to a CM5 chip. A new CM5 chip was inserted into the BIAcore and a sensorgram initiated with HBS buffer at a flow rate of 5 μl/min. The NHS and EDC coupling solutions (BIAcore) were mixed according to manufaeturer's instructions and 30 μl injected over the CM5 surface. Fifty μl of BLyS at 1 μg/ml in 10 mM sodium acetate buffer, pH4, was then injected followed by 30 μl of ethanolamine-HCl solution (BIAeore). The flow rate was then adjusted to 20 μl/min and 10 μl of 4M guanidine hydrochloride in HBS injected over the surface. This strips the surface of non-covalently bound BLyS.

Measurement of scFv off-rate kinetics on the low density surfaces

[0708] The chip containing the low density BLyS surface was inscrted in to the BIAcore. A dilution series of purified scFvs was prepared in HBS, typically 50 μg/ml doubling dilutions down to 1.5 ug/ml. The dilution series was then injected sequentially over the low density BLyS surface (and blank control) using the following program:

```
MAIN
FLOWCELL 1,2,3,4
APROG     genab     r1d1   ab1
APROG     genab     r1d2   ab2
APROG     genab     r1d3   ab3
APROG     genab     r1d4   ab4
APROG     genab     r1d5   ab5
APROG     genab     r1d6   ab6

APPEND CONTINUE
END

DEFINE APROG genab
PARAM %Abpos %AbId
FLOW      20
KINJECT   %Abpos 200 80
INJECT    r1c6 10!guanidine hydrochloride regeneration step
EXTRACLEAN
END
```

[0709] Bound scFvs were removed by injecting 10μl 4M GuHCl in HBS over the surface between scFv samples.

[0710] The binding curves for individual scFvs were analyzed using the BIAevaluation software to determine antibody off-rates. Kinetic analysis for a typical scFv antibody, I003C02, is shown in Figure 5. I003C02 has a $K_{off} = 6 \times 10^{-3}\ s^{-1}$.

Example 7: Inhibition in an In Vitro Receptor Binding Assay by scFv Antibodies

[0711] The 48 scFvs listed in Table 3 were purified and assessed for their ability to inhibit BLyS binding to its receptor on IM9 cells.

Purification of scFv

[0712] To determine the inhibitory potency of anti-BLyS scFv, scFv's were first prepared by IMAC. 2TYAG (5 ml) was inoculated with a single colony and grown overnight at 30°C, shaking. This overnight culture was then used to inoculate 500 ml of 2TY containing 100 μg/ml ampicillin and 0.1% Glucose, and grown at 30° C, shaking, until an A_{600} of 1.0 was attained. IPTG was added to 1 mM and the culture was grown for a further 3.5 hours at 30°C.

[0713] Cells were harvested by centrifugation at 5,000rpm, and resuspended in 10 ml of TES. A further 15 ml of a 1:5 dilution (in water) of TES was added, and the cell suspension incubated on a turning wheel at 4°C for 30 minutes. This causes osmotie shock and yields a periplasmic extract containing the scFv. Residual cells and debris were pelleted by centrifugation at 9,000 rpm for 20 minutes at 4°C. The supernatant was transferred to a new tube, and 50 μl of 1 M $MgCl_2$ added. Two ml of a Ni-NTA agarose (Qiagen), pre-washed with buffer (50 mM sodium phosphate, pH 8, 300 mM NaCl) together with a protease inhibitor tablet (Boehringer Mannheim) were then added to the periplasmic extract. The preparation was incubated, rotating, overnight at 4°C. The Ni-NTA was pelleted by centrifugation at 2,000 rpm for 5 minutes, and the supernatant was aspirated. The agarose beads were washed 3 times with 50 ml wash buffer, centrifuging to collect the agarose in between each wash. Ten ml of wash buffer was added after the final wash, and the slurry was loaded on to a polyprep column (BioRad). Two ml elution buffer (50 mM NaPi (sodium phosphate), pH 8, 300 mM NaCl, 250 mM imidazole) was added to the drained agarose, and the eluate was collected. IMAC purified scFv was buffer exchanged in to PBS by use of a Nap 5 column (Pharmacia) according to the manufacturer's instructions. The A_{280} was read and the protein concentration determined using a molar extinction coefficient of 1 mg/ml protein = A_{280} 1.4. Purified scFv was stored in 500 μl aliquots at -70°C.

Receptor Binding Inhibition Assay

[0714] Flat-bottomed 96-well plates (Costar) were coated with 100 μl per well of a 1:10 dilution of poly-L-lysine (Sigma) in PBS for 1 hour at room temperature. The plates were then washed twice with water, allowed to air-dry and placed at 4 °C overnight. One hundred μl of IM9 cells (at 10^6/ml in RPMI-1640) were then added to each well. Plates

were then centrifuged at 3200 rpm for 5 mins to pellet the cells. The media was carefully aspirated and 200 µl of MPBS added to each well. The plates were then left to block for 1 hour at room temperature.

[0715] To a separate 96-well plate, titrate test scFvs in MPBS, in triplicate, over a concentration range from 10 µg/ml down to 0.001 µg/ml were added. The final volume of test scFv in each well was 55 µl. Competition with unlabelled BLyS was also included in every assay as a control. Unlabelled BLyS, in MPBS, was typically titrated in triplicate, over a concentration range from 1 µg/ml down to 0.001 µg/ml. 10 µl of biotinylated-BLyS (at 162.5 ng/ml) in MPBS was added to each well to give a final concentration of 25 ng/ml. Plates were then incubated at room temperature for 30 minutes.

[0716] The IM9 coated plates was washed twice in PBS, tapped dry and immediately 50µl of the scFv/biotinylated-BLyS mix was added and incubated at room temperature for 1 hour. Plates were washed three times in PBST and three times in PBS, tapped dry and 50 µl per well added of streptavidin-Delfia (Wallac) at 1:1000 dilution in the Manufacturer's assay buffer. The plates were then incubated at room temperature for 1 hour and washed six times in Delfia wash solution (Wallac). After tapping the plates dry, 100µl per well of Delfia enhancement solution (Wallac) was added. The plates were gently tapped to encourage micelle formation, incubated at room temperature for 10 minutes, and fluorescence read on a Wallae 1420 workstation at 6520 nM.

[0717] Typical titration curves for two scFv antibodies, I007F11 and I050A07, are shown in Figure 6. Unlabelled BLyS competed for binding to its receptor with an IC_{50} value of 0.8 nM. The IC_{50} values for I007F11 and I050A07 are 7.9 nM and 17.1 nM , respectively. The assay was performed in triplicate and standard error bars are shown. The 9 scFvs that demonstrated the greatest inhibition as scFv are listed in Table 4. This data also confirms that these9 scFvs recognize the soluble form of BLyS.

Table 4: 9 ScFvs that demonstrated greatest potency in BLyS Receptor Binding Inhibition Assay

ScFv Antibody
I017D10

I022D01
I008A11
I006D08
I031F02
I050A12
I050B11
1051C04
I003F12S

Example 8: Antibodies recognizing a soluble form of BLyS

[0718] A library of phage was screened in an assay to identify those phage displaying scFvs that immunospecifically bind to the soluble but not the membrane-bound forms of BLyS.

[0719] A phage library was screened for the ability to bind to biotinylated BLyS. The phage were exposed to biotinylated BLyS, allowed an interval of time to bind the biotinylated BLyS. Phage binding bio-BLyS were then isolated by capture on streptavidin coated magnetic beads.

[0720] The phage identified in the screen above (capture of Bio-BLyS from solution) were then screened by ELISA for their ability to bind immobilized BLyS. The scFv expressed by phage that bound immobilized BLyS were then cloned and sequenced. Again, several sequences were identified multiple times, thus a panel (panel 2) consisting of on example of each phage expressing a unique scFv was then characterized further.

[0721] The derived amino acid sequences of these scFvs are shown in Table 1 above. The individual V_H and V_L segments of the scFvs were aligned to the known human germline sequences in V-BASE (Tomlinson et al, www.mrc-cpe.cam.ac.uk) and the closest germline identified.

Example 9: Specificity For Soluble BLyS

[0722] The scFvs were isolated from a library of phage based on their ability to bind a soluble form of BLyS. Briefly, phage were preincubated with biotinylated BLyS in solution. Phage that bound to this biotinylated BLyS were then isolated using streptavidin coated magnetic beads.

[0723] The specificity of each of the unique scFvs for BLyS and for the membrane-bound form of BLyS, was determined by phage ELISA. BLyS was immobilised onto plastic as a purified soluble form of the protein or as a membrane-bound form present on plasma membrane preparations from the human macrophage-like cell line, U937. Maintenance of U937 cells and plasma membrane preparations were performed as detailed in Example 2.

Phage ELISA

[0724] To determine the specificity of each of the scFvs, a phage ELISA was performed for each antibody against human BLyS, U937 plasma membranes, TNFα, BSA and an uncoated well. Antigen coating conditions were as described in Example 2, apart from human BLyS. BLyS was first biotinylated (as described in Example 3) and coated at 1 μg/ml onto streptavidin coated plates (Reacti-Bind, Pierce) for 30 mins at room temperature. The plates were then washed, blocked and the phage ELISA performed as detailed in Example 2.

[0725] The results for 3 clones (I074B12, I075F12 and I075A02) that bind the soluble but not the membrane-bound form of BLyS are shown in Figure 7. As a control, a phage antibody that recognizes TNFα, is also shown in Figure 7. There is a small non-specific background signal on the U937 plasma membranes that is evident with both the anti-BLyS scFvs as well as the anti-TNFα control. All 3 anti-BLyS scFvs recognize BLyS but not U937 plasma membranes, TNFα, BSA or an uncoated well (PBS only). This indicates that the scFvs do not bind the membrane-bound form of BLyS. Further, The fact that these scFvs were isolated on the basis of their ability to bind soluble biotinylated BLyS indicates that they bind the soluble form of BLyS. Further confirmation of these scFvs' specificity for BLyS is provided in Example 10.

Example 10: Inhibition in an in vitro receptor binding assay by phage scFvs

[0726] All of the unique phage scFvs from panel 2 were assessed for their ability to inhibit BLyS binding to its cognate receptor on IM9 cells. The biotinylation of BLyS, maintenance of IM9 cells and receptor binding inhibition assay were performed as described in Example 3.

[0727] Results for two phage scFvs, I0025B09 and I026C04 are shown in Figure 8. Maximal binding of biotinylated BLyS to its receptor (bio-BLyS only), the background signal in the absence of biotinylated BLyS (no bio-BLyS), and results with an irrelevant (i.e. does not recognize BLyS) phage antibody are also shown. Both phage scFvs inhibited biotinylated BLyS binding to its receptor on IM9 cells. 33 of the unique scFvs from panel 2 were identified for further study. These 33 scFvs demonstrated the greatest inhibition as phage particles in this assay and are listed in Table 5.

Table 5: Identification of 33 phage scFvs to free BLyS that demonstrate the most significant inhibition of biotinylated-BLyS binding to its receptor

Antibody	Antibody	Antibody	Antibody
I026C04	I074B12	I073F04	I065D04
I003C06	I075A02	I078D08	I068C08
I025B09	I068B08	I078D02	I068F03
I027B12	I068B04	I075G01	I069B07
I025B06	I068C06	I071B03	
I030A10	I075F12	I072B09	
I002A01R	I065D08	I078H08	
I002A01K	I065F08	I064C04	
I026C04R	I067B10	I064C07	
I026C04K	I067F05		

Example 11: Specificity of anti-BLyS scFvs

[0728] The specificity of the 33 scFvs (listed in Table 5) for immobilized human and murine BLyS was determined using phage ELISA.

Phage ELISA

[0729] To determine the specificity of the 33 scFvs, a phage ELISA was performed as described in Example 4 against human and mouse BLyS, and a panel of related human antigens: TRAIL, LIGHT, TNFα, TNFβ, and an uncoated well (PBS only).

[0730] Typical results for two scFvs, I067F05 and I078D02 are shown in Figure 9. A control antibody that specifically recognizes TNFα is also shown. Both anti-BLyS scFvs specifically recognize immobilized human and mouse BLyS but not any other antigen tested.

[0731] All 33 scFvs are specific for human BLyS. 14/33 cross-react with mouse BLyS but not with any other unrelated or related antigen tested.

Example 12: scFv Off-Rate Determinations

[0732] Off-rate determinations, preparation of a low density BLyS surface and kinetic measurements were as detailed in Example 6.

[0733] The binding curves for individual scFvs were analysed using the BIAevaluation software to determine antibody off-rates. Kinetic analysis for a typical scFv antibody, I002A01, is shown in Figure 10. I002A01 has a $K_{off} = 9 \times 10^{-4} s^{-1}$.

Example 13: Inhibition in an in vitro receptor binding assay by scFv antibodies

[0734] The 33 scFvs identified in Table 5 were prepared as purified scFvs and assessed for their ability to inhibit BLyS binding to its receptor on IM9 cells. The scFvs were purified and analysed in the receptor binding inhibition assay as described in Example 6.1.8.

[0735] Typical titration curves for two scFvs, I0068C06 and I074B12, are shown in Figure 11. Unlabelled BLyS competed for binding to its receptor with an inhibitory constant 50 (IC_{50}) value of 0.66 nM. The IC_{50} values for I0068C06 and I074B12 are 61 nM and 13 nM , respectively. The assay was performed in triplicate and standard error bars are shown. The 7 scFvs that demonstrated the greatest inhibition as scFv are listed in Table 6.

Table 6: Identification of 7 scFvs to free BLyS that demonstrate the most significant inhibition of biotinylated-BLyS binding to its receptor as purified scFv's.

Antibody
I002A01-R
I002A01-K
I026C04-R
I026C04-K
I068C06
I075F12
I067B10

Example 14: ScFvs Recognizing Membrane-bound BLyS

[0736] A library of phage was screened in an assay to identify those phage displaying scFvs that immunospecifically bind to the membrane-bound but not the soluble form of BLyS.

[0737] As a starting point, a library of phage expressing scFv antibodies were panned on immobilized HIS-tagged BLyS. Phage isolated by panning were then screened for the ability to bind to HIS-tagged BLyS. HIS-tagged BLyS was obtained by expressing amino acids 71-285 of SEQ ID NO:3228 using the pQE9 vector (Qiagen Inc., Valencia, CA) in *E. coli* and purifying the expressed protein. This phage clones identified by this screen were then sequenced. After sequencing, A panel (panel 3) of phage each expressing a unique scFv that bound HIS-tagged BLyS was generated and further characterized.

[0738] The derived amino acid sequences of the unique scFvs from panel 3 are shown in Table 1 above. The individual V_H and V_L segments of the scFvs were aligned to the known human germline sequences in V-BASE (Tomlinson et al, www.mrc-cpe.cam.ac.uk) and the closest germline identified.

Example 15: Recognition of Membrane-bound BLyS

[0739] The specificity of each of the unique scFvs for both the membrane-bound form of BLyS as well as for the soluble form of BLyS, was determined by phage ELISA.

[0740] BLyS was immobilised onto plastic either directly as a purified soluble form of the protein or biotinylated and coated on a streptavidin plate as in Example 9. Binding to HIS-tagged BLyS was used as a primary screen for scFv's that would bind the membrane-bound form of BLyS (see below). The membrane-bound form of BLyS was presented as plasma membranes preparations from the human macrophage-like eell line, U937 or the murine cell line P388.

[0741] Mouse monoclonal antibodies have been raised against His-tagged BLyS according to standard procedures. Characterization of these mouse monoclonal antibodies revealed that they specifically recognized both His-tagged BLyS and the membrane-bound form of BLyS on U937 cells, but not soluble BLyS. Therefore, specific recognition of His-tagged BLyS was used as supporting evidence for the recognition of the membrane-bound form of BLyS by phage and scFv antibodies.

Phage ELISA

[0742] To determine the specificity of each of the scFvs, a phage ELISA was performed for each antibody against His-tagged human BLyS, U937 plasma membranes, TNFα, BSA and an uncoated well. Antigen coating eonditions were as described in 2. apart from human BLyS. BLyS was first biotinylated (as deseribed in Example 3) and coated at 1 μg/ml onto streptavidin coated plates (Reacti-Bind, Pierce) for 30 mins at room temperature. The plates were then washed, blocked and the phage ELISA performed as detailed in Example 2.

[0743] The results for 3 clones, I079C01, I081C10 and I082A02, and a control phage antibody that recognizes TNFα, are shown in Figure 12. All 3 scFvs recognize U937 plasma membranes (U937) and His-tagged BLyS (HIS-BLyS) but not, biotinylated BLyS (bio-BLyS) or an uncoated well (PBS). This indicates that the seFvs recognize the membrane-bound form of BLyS.

Example 16: Specificity for Membrane-bound BLyS

[0744] The specificity of the scFvs for only the membrane-bound form of BLyS, and not for the soluble form, was confirmed using a competition ELISA. This assay assesses the ability of test phage scFvs to bind to the membrane-bound form of BLyS on U937 plasma membranes in the presence of different forms of competing BLyS. Competing BLyS was either the His-tagged form of BLyS or soluble BLyS. ScFvs specific for the membrane-bound BLyS would be expected to be competed out by pre-incubation with His-tagged BLyS but not by pre-incubation with soluble BLyS.

[0745] Maintenance of U937 cells and plasma membrane preparations were performed as detailed in Example 2.

Competition ELISA

[0746] U937 plasma membranes (50μl per well) were coated at 10μg/ml in PBS onto Falcon 96-well plates overnight at 4°C.

[0747] Individual E. coli colonies containing a phagemid representing one of the unique scFvs from the panel 3 were inoculated into 50 ml tubes (Falcon) containing 5 ml 2TYAG medium. Tubes were incubated at 37°C for 4 hours, shaking. M13KO7 helper

phage was added to each tube to an MOI of 10 and the tubes were incubated for a further 1 hour at 37°C. The tubes were centrifuged in a benchtop centrifuge at 3500 rpm for 10 minutes. The supernatant was removed and cell pellets were resuspended in 5 ml 2TYAK and incubated at 30°C overnight, shaking. The next day, tubes were centrifuged at 3500 rpm for 10 min and the phage-containing supernatant carefully transferred into a fresh tube.

[0748] For each test phage antibody, 3 aliquots of 20μl 18% marvel/6xPBS were transferred into separate wells of a 96-well plate. The first aliquot was supplemented with His-tagged BLyS to a final concentration of 60 μg/ml. The second aliquot was supplemented with soluble BLyS to a final concentration of 60 μg/ml. The third aliquot was not supplemented with any competing antigen. One hundred μl of phage supernatant was then added to each aliquot and left to block at room temperature for 1 hour.

[0749] The antigen-coated plates were washed once with PBS before the addition of 200 μl/well 3% marvel/PBS. These plates were left to block at 37°C for 1 hour and were then washed once with PBS. Duplicate samples of 50 μl pre-blocked phage (above) were added to the antigen-coated plates and left at room temperature for 1 hour. Plates were washed 3x with PBS/0.1%Tween 20, then 3x with PBS. Fifty μl/well mouse anti-M13 HRP (Pharmacia) at 1/5000 in 3% Marvel/PBS was added and left for 1 hour at room temperature. Plates were washed 3 times with PBS/0.1%Tween 20, then 3 times with PBS. Fifty μl/well HRP-labelled anti-mouse Envision polymer (DAKO) at 1/50 in 3% marvel/PBS was added and left for 1 hour at RT. Plates were washed 3 times with PBS/0.1% Tween 20, then 3 times with PBS. Next, 50μl/well of TMB (Sigma) was added and plates left to develop for 30 to 60 minutes. When sufficient color has developed, 25μl/well 0.5M H_2SO_4 was added to stop the reaction. The plates were read at 450nm on a microtiter plate reader (Bio-Rad 3550).

[0750] The results for 3 clones, I079B04, I079F08 and I080B01, and a control phage antibody that recognizes TNFα, are shown in Figure 13. All 3 scFvs recognize U937 plasma membranes (U937). This binding is competed out to background levels (i.e. comparable to the signal observed with the anti-TNFα phage antibody) in the presence of His-tagged BLyS (HIS-BLyS) but not biotinylated BLyS (bio-BLyS). This confirms that

the scFvs specifically recognize the membrane-bound form but not the soluble form of BLyS.

Example 17: High Throughput BIAcore Screen to identify high affinity scFvs

[0751] This is a 96-well screen where the test samples (scFvs) are derived from 1 ml periplasmic extracts of individual antibody expressing clones. Potentially higher affinity scFvs are then identified principally as those giving a large number of total RU's bound to a HIS-BLyS surface in BIAcore. This method of ranking does assume approximately equal yields of scFv from each clone. Since this is not always the case, some scFvs may also be identified that simply express high levels of scFv. These can be discriminated from those of higher affinity by further characterization of the scFvs (see Example 18).

Preparation of ScFv from 1ml E.coli Cultures

[0752] Individual E.coli colonies containing a phagemid representing one of the unique scFvs from panel 3 were inoculated into 96-well plates containing 100 μl 2TYAG medium per well. Eight wells on each plate were reserved for positive and negative control samples. The plate was grown overnight at 30°C with shaking at 120 rpm.

[0753] Next day, 1ml of 2TYAG + 345 mM sucrose was added to each well of an autoclaved 96 deep well plate (Beckman). Twenty μl of each overnight culture was resuspended and transferred to the appropriate well of the deep well plate. The plate was grown for approximately 3.5 hours at 30°C with shaking at 250 rpm (or until the OD_{600} = 0.6). Fifty μl of 1M IPTG was added to 5ml 2TY and 10μl of this was added to each well. The plate was grown overnight at 30°C with shaking at 250rpm.

[0754] Plates were kept at 4°C for the remainder of the procedure. The overnight plate (above) was centrifuged at 3500 rpm for 10 minutes at 4°C to pellet the cells. The supernatant was decanted and each pellet resuspended in 100μl TES (0.2M Tris HCl pH8.0, 0.5mM EDTA, 0.5M sucrose) and transferred to a fresh 96 well plate. This plate was incubated on ice for 30 minutes and then centrifuged for 10 minutes at 3500 rpm at 4°C to pellet the cell debris. During centrifugation, 15μl of freshly made protease inhibitors cocktail (Roche, 1 tablet dissolved in 1.5 ml water) was added to each well of a fresh 96 well plate. Supernatants from the centrifuged plate were then transferred to the plate containing the protease inhibitors. The plate was centrifuged at 3500 rpm for 10

minutes at 4°C and the supernatant was transferred to a further 96-well plate. This step was repeated at least once more or until there was no sign of any cell debris following centrifugation. Finally, the plate was covered in foil to prevent evaporation of samples during the BIAcore run.

Generation of a high density HIS-BLyS surface

[0755] All BIAcore analysis was performed on BIAcore 2000 machines, using the BIAcore 2000 control software and evaluated using the BIAevaluation 3.0 software. A high density His-tagged BLyS surface (>1000 RU HIS-BLyS coupled) was prepared in flow cell 2 by amine coupling to a CM5 chip. A new CM5 chip was inserted into the BIAcore and a sensorgram started over flow cell 2 with HBS buffer at a flow rate of 5μl/min. The NHS and EDC solution were mixed 1:1 before injecting 30μl over the CM5 surface. Fifty μl HIS-BLyS (at 10μg/ml in Sodium acetate buffer, pH4) was injected and allowed to couple to the surface. Thirty μl of ethanolamine-HCl solution was then injected to block free NHS esters. Prior to using the chip, 10μl of 4M Guanidine hydrochloride in HBS was injected over the surface to strip the surface of non-covalently bound BLyS. A blank surface (no HIS-BLyS) was also prepared over flow cell 1 so that non-specific binding effects can be subtraeted from the HIS-BLyS binding curves.

[0756] Typically, a 5000 RU His-tagged BLyS surface was generated in this way and used for 96-well analysis of scFvs isolated from the periplasm of E.coli.

BIAcore Analysis

[0757] The 96-well plate containing periplasmic scFvs was secured inside the BIAcore. Two ml of 4M Guanidine hydrochloride in HBS was placed in a rack inside the BIAcore for regeneration of the HIS-BLyS surface between samples. The sensorgram was run over flow cells 1 and 2 at a flow rate of 20μl/minute. The following method was run:

MAIN

FLOWCELL 1,2,3,4

LOOP cycle STEP

```
APROG inj %pos
ENDLOOP
APPEND CONTINUE
END

DEFINE LOOP cycle
LPARAM %pos

r1a1
r1b1
r1c1
r1d1
r1e1
r1f1 etc (all wells listed until r1h12)

END
DEFINE APROG inj
PARAM %pos
FLOW 20
KINJECT %pos 35 30 !scfv injection
QUICKINJECT r2f3 10 !regeneration
EXTRACLEAN
END
```

[0758] When the run had finished, the sensorgram data for flow cell 1 was subtracted from the data for flow cell 2 for each sample using the BIAevaluation software. The clones were compared with one another principally by overall RU change as the scFv dissociates from the surface. In addition a few scFvs were identified as having potentially slower off-rates. An example of the dissociation section of a typical sensorgram for 8 scFvs is shown in Figure 14. An anti-TNFα antibody that does not recognize BLyS was included as a control. Of the 8 scFvs exemplified, I079F06 was identified for further study due to the relatively high numbers of RU's bound to the surface.

[0759] ScFvs were identified principally if they demonstrated a RU change of over 1200, a few were also identified as having potentially slower than typical off-rates. A total of 28 clones were chosen on these criteria and are listed in Table 7.

Table 7: Identification of 28 antibodies to membrane-bound BLyS that demonstrate the most significant RU changes by BIAcore

Antibody	Antibody
I079C01	I084C04
I082H08	I080E05
I079E02	I083B12
I079B05	I082G01
I079F06	I082G02
I079F08	I082C03
I079F11	I082A05
I079B12	I082D07
I080B01	I082B08
I080G09	I084A01
I099D03	I084B02
I080D03	I080A08
I080A03	I084C11
I083G03	
I080G07	

Example 18: scFv Affinity Determinations

[0760] The affinity (K_D) of the 28 scFvs was determined using the BIAcore.

Low Density HIS-BLyS Surface for Kinetic Studies

[0761] 500RU surfaces were used for kinetic studies of purified scFv binding to HIS-BLyS. The method to prepare these surfaces was identical to the method described in Example 17, only smaller volumes of HIS-BLyS were injected.

Measurement of scFv Binding Kinetics

[0762] The chip containing the low density HIS-BLyS surface was inserted into the BIAcore. A dilution series for each of the 28 purified scFvs (prepared as in Example 6) were diluted in HBS (typically starting with 50μg/ml scFv and double diluting down to

1.5μg/ml). The dilution series was then injected sequentially over the blank control (flow cell 1) and low density HIS-BLyS surface (flow cell 2) using the following program:

```
MAIN
FLOWCELL 1,2,3,4
APROG     genab     r1d1   ab1
APROG     genab     r1d2   ab2
APROG     genab     r1d3   ab3
APROG     genab     r1d4   ab4
APROG     genab     r1d5   ab5
APROG     genab     r1d6   ab6

APPEND CONTINUE
END

DEFINE APROG genab
PARAM %Abpos %AbId
FLOW        20
KINJECT     %Abpos 200 80
INJECT      r2f3 10
EXTRACLEAN
END
```

[0763] Bound scFv were removed by injecting 10μl of 4M Guanidine hydrochloride in HBS (location r2f3 in the above program) over the surface between samples. Binding curves for individual scFv were analysed using the BIAevaluation software to determine antibody on- and off-rates.

[0764] A typical example of the binding curves generated for the scFv antibody I082C03 is shown in Figure 15. The off-rate for this clone was calculated as $2x10^{-3}$ s^{-1}. The affinity of I082C03 was calculated as 20 nM, assuming 100% activity of the scFv. The 5 scFvs with the highest affinities as scFvs are given in Table 8.

Table 8: Identification of 5 antibodies to membrane-bound BLyS that have the highest affinities as scFvs

Antibody	Affinity (K_D)
I079F11	5nM
I079E02	10nM
I082G02	6nM
I082H08	1nM
I099D03	4nM

Example 19: Recognition of mouse membrane-bound BLyS

[0765] The ability of the 5 scFvs listed in Table 8 to also recognize murine membrane-bound BLyS was determined using a competition ELISA. This assay assesses the ability of test phage scFvs to bind to the membrane-bound form of BLyS on the murine cell line, P388, plasma membranes in the presence of different forms of competing human BLyS. Competing BLyS was either presented as the His-tagged form of BLyS, or soluble BLyS. ScFvs that recognize mouse membrane-bound BLyS would give an ELISA signal on the P388 plasma membranes that is competed out by pre-incubation with HIS-tagged BLyS but not by pre-incubation with soluble BLyS.

Maintenance of P388.D1 cells and preparation of plasma membranes

[0766] P388.D1 cells are a mouse monocyte-macrophage like cell line. They were cultured in L-15 medium supplemented with 2mM L-glutamine, 10% CS, 10U penicillin, 100g/ml streptomycin (all reagents from Sigma). Cells were split 1:4 every 3-4 days to maintain a cell density of 2-8 x 10^5 per ml. A fresh aliquot of cells was thawed from liquid nitrogen every 6 weeks. Plasma membrane fractions were prepared as described in Example 2.

Competition ELISA

[0767] P388 plasma membranes (50μl per well) were coated at 10μg/ml in PBS onto Falcon 96-well plates overnight at 4°C. The method is otherwise essentially as described Example 16.

[0768] The results for 3 clones, I079E02, I082H08 and I099D03 are shown in Figure 16. All 3 scFvs recognize P388 plasma membranes. This binding is competed out in the presence of HIS-tagged BLyS (HIS-BLyS) but not in the presence of biotinylated BLyS (bio-BLyS). This confirms that these scFvs also recognize the membrane-bound form but not the soluble form of mouse BLyS.

Example 20 : Conversion of scFvs to IgG1 format

[0769] The VH domain and the VL domains of scFvs that we wished to convert into IgG molecules were cloned into vectors containing the nucleotide sequences of the appropriate heavy (human IgG1) or light chain (human kappa or human lambda) constant regions such that a complete heavy or light chain molecule could be expressed from these vectors when transfected into an appropriate host cell. Further, when cloned heavy and light chains are both expressed in one cell line (from either one or two vectors), they can assemble into a complete functional antibody molecule that is secreted into the cell culture medium. Methods for converting scFvs into conventional antibody molecules are well known within the art.

Generation of NS0 cell lines expressing anti-BLyS antibodies (IgG1)

[0770] Plasmids containing the heavy and light chains were separately linearized using the Pvu I restriction enzyme. The linearized DNAs were purified by phenol-chloroform extraction followed by ethanol precipitation and then resuspended in H_2O. NS0 cells (10^7) from a growing culture were electroporated (0.25kV and 975μF) in PBS with 12.5 μg linearized heavy chain plasmid DNA and 37.5 μg linearized light chain DNA. The cells were washed in 20 ml non-selective medium (10% FCS in DMEM supplemented with 6mM glutamine, amino acids and penicillin/streptomycin) and then transferred in 12.5 ml medium into a T75cm^2 flask and incubated overnight at 37°C, 5% CO_2/air. The day after transfection the cells were resuspended in selective medium containing 1mg/ml geneticin and dispensed into 5 x 96-well plates at 200 μl/well. After 18 days at 37°C (5% CO_2/air) the colony supernatants were screened by an ELISA that detects assembled human IgG in order to identify colonies expressing IgG. Approximately twenty positive colonies were expanded and adapted to growth in serum-free, selective medium. Duplicate T25cm^2 flasks were set up. Cells from one flask were frozen down as a stock and cells in the

second flask were grown to saturation. The productivity of the saturated cultures was assessed by ELISA. The highest producing cell lines were then selected for large-scale antibody production.

[0771] The above procedure is exemplified for the I006D08 anti-BLyS antibody constructs. Following electroporation and selection of NS0 cells, supernatants from ninety-three wells each containing a single colony were screened by ELISA to detect assembled IgG1, antibody. Twenty-seven of the supernatants were identified as eontaining IgG. The colonies from 24 of the positive wells were transferred to 1ml selective medium in a 24-well plate and allowed to grow for 2 days. The 1ml cultures of cells were then added to 4ml selective medium containing reduced serum (0.5% FCS) in a T25cm^2 flask. When the cultures reached confluency 1 ml cells were diluted in 4ml selective, serum-free medium in a T25cm^2 flask. At confluency this subculture regime was repeated again. Finally 1ml cells from the culture containing 0.1% FCS was diluted with 9 ml serum-free, selective medium and divided into 2 x T25cm^2 to form the saturated and stock eultures. The stock cultures were frozen down and stored in liquid nitrogen once the cultures were confluent. The saturation culture was grown until the viability of the culture was < 10%. Twenty-three out of the 24 colonies originally expanded were successfully adapted to growth in serum-free medium. The productivity of these serum-free adapted cell lines ranged from 0.3 to 17 μg/ml by ELISA quantification of the saturated, 5ml serum-free cultures. The I006D08-32 cell line produced 17 μg/ml.

Large-scale IgG production

[0772] The highest-producing cell lines were revived from frozen stocks and then expanded to 400ml in selective, serum-free medium in 2 liter roller bottles. The cells were grown at 37°C and rolled at 4 rpm with the headspace being re-equilibrated with 5% CO_2/air every 2-3 days. Finally the culture was expanded to a 4 liter volume by the addition of serum-free medium without selection (400 ml per 2 liter roller bottle). The cultures were then grown to saturation.

[0773] This procedure is exemplified by the production of I006D08 antibody from the I006D08-32 cell line. The frozen stock of I006D08-32 was revived into a T25 cm^2 containing 5 ml serum-free medium containing 1mg/ml geneticin and grown at 37°C in 5% CO_2/air incubator. After two days growth the culture was diluted with 7.5 ml fresh

medium and transferred to a T75cm^2 flask. After a further three days in the incubator the cells were transferred to 130 ml selective medium and transferred to a 2 liter roller bottle. After three days growth the cells were diluted with 500 ml selective medium and split into 2 x 2 liter roller bottles. After another 2 days 100 ml fresh selective medium was added to each roller. Finally the next day the culture was expanded to a total volume of 4 liters with non-selective medium and divided into 10 x 2 liter roller bottles. After three days the medium was supplemented with 6mM glutamine. The cells were grown for 17 days from the final subculture into a 4 liter volume. The cells grew up to 3 x10^6 cells/ml before viability declined to < 0.2 x 10^6 eells/ml. At this low viability the culture supernatants were harvested. ELISA analysis indicated that the culture supernatant contained 33 μg/ml IgG. Henee, the 4 liter eulture contained 132 mg IgG.

IgG Purification

[0774] The purification of the IgG from the fermentation broth is performed using a combination of conventional teehniques commonly used for antibody production. Typieally the culture harvest is clarified to remove eells and cellular debris prior to starting the purifieation scheme. This would normally be achieved using either centrifugation or filtration of the harvest. Following elarification, the antibody would typically be eaptured and significantly purified using affinity ehromatography on Protein A Sepharose. The antibody is bound to Protein A Sepharose at basic pH and, following washing of the matrix, is eluted by a reduction of the pH. Further purification of the antibody is then achieved by gel filtration. As well as removing components with different molecular weights from the antibody this step can also be used to buffer exchange into the desired final formulation buffer.

Purification of I006D08 IgG1

[0775] The harvest was clarified by sequential filtration through 0.5 μm and 0.22 μm filters. Clarified harvest was then applied to a column of recombinant Protein A Sepharose equilibrated at pH 8.0 and washed with the equilibration buffer. I006D08 antibody was eluted from the Protein A Sepharose by application of a buffer at pH3.5. The collected antibody containing eluate was then neutralized to pH 7.4 by the addition of pH 8.0 buffer. The neutralized eluate was concentrated by ultrafiltration using a 30 KDa cut off

membrane. Concentrated material was then purified by Sephacryl S300HR gel filtration using phosphate buffered saline as the mobile phase. The final monomeric IgG1 fraction from the gel filtration column was then concentrated to the desired formulation concentration by ultrafiltration using a 30 KDa cut off membrane. The final product was filtered through a 0.22 μm filter.

Example 21: Antibody neutralization of murine splenocyte proliferation as measured by 3HdT incorporation

[0776] To determine if an antibody inhibited BLyS mediated B eell proliferation, a splenocyte proliferation assay was performed Briefly, murine splenocytes were isolated by flushing spleen using a 25g needle and 10 ml of complete medium (RPMI 1640 with 10% FBS containing 100U/ml penicillin, 100μg/ml streptomyein, 4mM glutamine, $5x10^{-5}$M β-mercaptoethanol). The cells were passed through a 100 micron nylon filter to remove cell clumps. The cell suspension was then ficolled at 400 x g for 25 minutes at room temperature (one 15 ml conical tube/spleen; 3 ml ficol, 10 ml cell suspension/spleen; Ficol 1083 from Sigma). The recovered cells were washed 3 times in complete medium and counted. Recovered cells were then diluted to a concentration of $3x10^6$/ml in complete medium containing a 3X concentration of SAC (3X = 1:33,333 dilution of stock; stock is a 10% suspension of Staph. aureus (Cowan I strain) available from Calbiochem).

[0777] For each antibody, 50 microliters of antibody dilutions at 30μg/ml, 3.0μg/ml, and 0.3μg/ml concentrations were aliquotted into individual wells of a 96 well plate in triplicate. Suitable positive controls, such as, for example monoclonal antibody 15C10, were also used. Antibody 15C10 is described in Moore et al., (1999), *Science* 285: 260-263 and WO0050597; 15C10 has also been deposited with the ATCC on February 1, 2000 as ATCC Deposit No. PTA-1158. Medium containing no antibody (and human isotype controls (purchased commercially) when necessary) were used as negative controls.

[0778] BLyS protein was diluted in complete medium to concentrations of 300ng/ml, 90ng/ml and 30ng/ml. 50 microliters of eaeh of the BLyS dilutions were then added to the antibody dilution series in the plates. The plate containing the antibody and BLyS dilutions are then incubated for 30 minutes at 37°C, 5% CO_2, after which 50 microliters of the splenocyte cell suspension containing SAC was added to all wells. The plates were then incubated for 72 hours (37°C, 5% CO_2).

[0779] After 72 hours, each well was supplemented with 50µl of complete medium containing 0.5µCi of 3H-thymidine (6.7 Ci/mM; Amersham) and cells were incubated for an additional 20-24 hours at (37°C, 5% CO_2). Following incubation cells were harvested using a Tomtec Cell Harvester and filters counted in a TopCount Scintillation counter (Packard).

Example 22: Human B cell proliferation assay for in vitro screening of BLyS antagonist molecules

[0780] The bioassay for assessing the effects of putative BLyS antagonists was performed in triplicate in 96 well format by mixing equal volumes of BLyS, responder cells, and putative antagonist each of which is prepared as a 3X stock reagent.

[0781] B-lymphocytes were purified from human tonsil by MACS (anti-CD3 depletion), washed, and resuspended in complete medium (CM) (RPMI 1640 with 10% FBS containing 100U/ml penicillin, 100µg/ml streptomycin, 4mM glutamine, 5x10E-5 M beta-mercaptoethanol) at a concentration of 3 x 10e6 cells/mL. *Staphylococcus aureus,* Cowan I (SAC, CalBiochem) was added to cells at 3X concentration (3X = 1:33,333 dilution of stock

[0782] Meanwhile, eight serial dilutions (3-fold) of potential antagonist were prepared in CM sueh that the diluted antagonists are at 3X the final concentrations to be tested in the assay. Antibodies are routinely tested starting at a final concentration of 10ug/mL and going down to about 1.5 ng/mL.

[0783] Human rBLyS was prepared in CM to 3X concentration (3X = 300 ng/mL, 30 ng/mL, and 3 ng/mL) in CM. Potential inhibitors were routinely tested at several concentrations of BLyS to avoid false negatives due to unexpectedly low affinity or antagonist concentration.

[0784] Fifty microliters of diluted antagonist and 50uL of diluted BLyS were added to the putative antagonist dilution series.

[0785] Cells were then incubated for 72 hours (37°C, 5% CO_2) in a fully humidified chamber. After 72 hrs., the cells were supplemented with 0.5 µCi/well 3H-thymidine (6.7 Ci/mmol) and incubated for an additional 24 hours. Plates were harvested using a Tomtec Cell Harvester and filters counted in a TopCount Scintillation counter (Packard).

Example 23: Characterization of I006D08 and I116A01

[0786] I116A01 (SEQ ID NO:327) is a CDR3 mutant of the I006D08 (SEQ ID NO:2). The I116A01 scFv was subsequently isolated from a single chain phage display library containing a repertoire of I006D08 mutations generated by randomization of the last 6 amino acids of the heavy chain CDR3 region of I006D08. The I116A01 scFv contains 7 amino acid differences from the parental I006D08 sequence, 1 change in the VH framework 3 region, 5 changes in the VH CDR3, and 1 change in the VLCDR3. Each of the assays described herein were performed using whole IgG1 molecules comprising the VH and VL regions of I006D08 and I116A01.

Binding studies of I006D08 and I116A01

[0787] Equilibrium dissociation constants (Kd) for I116A01 and I006D08 binding to BLyS were assessed using BIAcore technology (BIAcore, Uppsala, Sweden). Briefly, antibodies were captured on low-density Protein A surfaces and BLyS was passed over at various flow rates. The binding of BLyS to immobilized antibody was detected by changes in surface charge that were proportional to the amount of bound BLyS. Binding values were calculated using software provided by the manufacturer.

[0788] I116A01 was determined to have an equilibrium dissociation constant, Kd, of 267 ± 70 pM (mean ± SD, n=3). The Kd value of I006D08, the parental antibody, was determined to be 498 ± 151 pM (mean ± SD, n=3). This was approximately 2-fold higher than the Kd obtained for I116A01. The difference in affinity can be attributed to a 2-fold higher off rate (*k*d, 1/s) of I006D08 compared with I116A01, the on rates (*k*a, 1/Ms) being essentially equal (Table 9).

Table 9 Kinetic parameters for I116A01 and I006D08 binding to BLyS

Mab	*k*a, 1/Ms Mean ± SD	*k*d, 1/s Mean ± SD	Kd, pM Mean ± SD
I116A01	$1.26 \pm 0.14 \times 10^{6}$	$3.32 \pm 0.63 \times 10^{-4}$	267 ± 70
I006D08	$1.43 \pm 0.13 \times 10^{6}$	$5.8 \pm 0.24 \times 10^{-4}$	498 ± 151

[0789] The Kd values obtained for the BLyS antibodies indicate that these antibodies bind to BLyS with high affinity and possess a slow dissociation or off rate.

[0790] The binding characteristics of I116A01 and I006D08 were investigated further using a competitive binding ELISA in which BLyS was immobilized directly on the surface of the well to compare epitopes. Biotinylated I006D08 binding was inhibited in a dose-dependent manner by the addition of unlabeled I006D08 or I116A01 suggesting that these antibodies recognize overlapping or identical epitopes on BLyS.

Ability of I006D08 and I116A01 to inhibit BLyS-induced spelnocyte proliferation

[0791] The ability of I006D08 and I116A01 to inhibit BLyS-induced spelnocyte proliferation was tested using the assay described in Example 21 with slight modifieations. In particular, the assay was modified such that the final concentration of BLyS in the assay was 3ng/ml and the final dilution factor of SAC was 1:100,000. Using this assay it was shown that both antibodies I006D08 and I116A01 were each found to inhibit murine splenocyte proliferation induced by both human (aa134-285 of SEQ ID NO:2) and murine soluble BLyS. The IC_{50} values for the inhibition of human BLyS induced-proliferation of murine B cells was 0.09 nM ± 0.01 nM and 0.06 nM ± 0.01 nM, respeetively.

Additional characterization of I006D08 and I116A01

[0792] I006D08 and I116A01 were identified herein as antibodies that bind both the membrane bound and soluble forms of BLyS. The ability to bind the membrane bound form of BLyS was determined according to the assays described above, e.g., ability to bind HIS-tagged BLyS and ability to bind U937 and/or P388 membrane preparations in an ELISA assay. Further characterization of antibodies I006D08 and I116A01 reveals that these antibodies bind recombinant BLyS polypeptides expressed on the surface of a 293T cell. On the other hand, these antibodies are not able to bind naturally occurring BLyS (non-reeombinant) expressed on the surface of a cell, e.g., K-562 cells (ATCC #CCL-243) or U-937 eells (ATCC #CRL-1593.2). Thus, I006D08 and I116A01 bind the soluble form of BLyS. I006D08 and I116A01also bind the membrane bound form of BLyS (as determined by their ability to bind HIS-tagged BLyS and their ability to bind U937 and/or P388 membrane preparations in an ELISA assay). I006D08 and I116A01 also bind recombinant BLyS expressed on the surface of a 293T transfected fibroblast cell line, but do not bind naturally oceurring BLyS protein on the surface of a K-562 or U-937 cell.

Example 24: In Vivo studies of Anti-BLyS antibodies

[0793] Overexpression of BLyS in transgenic animals results in an autoimmune phenoptype including increased numbers of mature B cells (leading to enlarged spleens), increased levels of serum immunoglobulins, as well as increased levels of autoantibodies (e.g., anti-dsDNA antibodies) (McKay et al., (1999), The Journal of Experimental Medicine 190:1697-1710 and Gross et al., (2000) Nature 404:995-999, both of which are hereby incorporated by reference in their entireties.) Similar effeets are observed when recombinant BLyS is administered to animals such as mice and monkeys. The ability of anti-BLyS antibodies of the invention to reduce or prevent these BLyS induced effects may be tested through either co-adminstration or sequential admintration of soluble BLyS and anti-BLyS antibodies of the invention in an animal. An anti-BLyS antibody of the invention would be considered neutralizing if it prevented or reduced BLyS-induced increases in B cell numbers (resulting in lack of, or less, enlargement of spleen), and serum immunogloblins, and in particular serum autoantibodies.

Example 25: Antibody Production and Purification

[0794] The following example describes a large scale antibody production and purification methods that can be used to make antibodies of the present invention. One of skill in the art will be aware of routine modifications to the protocol described below, for example, as regards column choice, column, loading, wash, and elution buffers, and pH.

Cell Culture Scale-up and Antibody Production

[0001] A serum-free and animal source-free growth medium is used from thawing cells through scale-up to the production bioreactor. The growth medium is prepared by adding 1 kilogram AGT powder granules preformulated with GS supplement to water for injection (WFI) quality water making a total of 51 kilograms CD hybridoma medium. To the CD hyrbridoma medium, 1 mL/kg cholesterol (synthetic) lipid coneentrate (1000X). The AGT powder granules preformulated with GS supplement for preparing the CD hybridoma medium and the synthetic cholesterol lipid concentrate and are available from Invitrogen Corp., Carlsbad, CA. The medium, hereinafter referred to as INV-CDH medium, is stored at 2-8°C until use.

Thawing cells from into Spinner Flask

[0795] Approximately 48 x 10^6 NS0 cells engineered to express an antbody of the invention, preferably in whole IgG1 format, are thawed at 37°C in a water bath. The cells are transferred into a 250 mL spinner flask to yield approximately a 150 mL working volume with an inoculation density of approximately 3.2 x 10^5 cells/mL. The spinner flask(s) is then placed on magnetic stirrers in a humidified CO_2 incubator at 37°C with 5% CO_2 for 4 days. The agitation rate for the spinner flask is 80 rpm.

First Expansion(s) of Culture in Spinner Flask

[0796] The culture is aseptically expanded into a 1000 mL spinner flask to give approximately 600 mL working volume, at an inoculation cell density of approximately 2.5 x 10^5 cells/mL. The spinner flask is then placed on magnetic stirrers in a humidified CO_2 incubator at 37°C with 5% CO_2 for 3 days. The agitation rate for the spinner flask is 80 rpm.

[0797] The culture is again expanded aseptically into two 3000 mL spinner flasks to give approximately 2 x 2000 mL working volume, at an inoculation cell density of approximately 3.0 x 10^5 cells/mL. The spinner flask is then placed on magnetic stirrers in a humidified CO_2 incubator at 37°C with 5% CO_2 for 3 days. The agitation rate for the spinner flasks is 80 rpm. At the same time, a reserve culture is created in a fresh 250 mL spinner flask. The reserve culture may be used as the seed for another lot as needed.

Seed Culture (25 Liters)

[0798] The 25 liter seed bioreactor is equipped with one impeller for mixing, a dissolved oxygen probe, a temperature probe, a pH probe, aseptic sampling and additional systems. The first step of the cell cultivation process is the addition of INV-CDH medium into the bioreactor. After the medium temperature reaches 37 ± 0.5°C, the dissolved oxygen (DO) and pH levels are stabilized by addition of N_2 and CO_2 to decrease dissolved oxygen concentration to 25 to 75% air saturation, and obtain a pH of 7.20 ± 0.2. The agitation rate is 70 rpm. The pooled cell culture is transferred aseptically to the 25 liter seed bioreactor containing 21 liters of sterile INV-CDH medium. During the cultivation process the temperature is maintained via a plant stem and chilled glycol, which regulate

the temperatire of the circulating jacket. The oxygen concentration is maintained via oxygen and nitrogen sparging and surface aeration, and pH is controlled by addition of CO_2 gas to lower the pH. The cultivation period is 4 days. The bioreactor air/gas inlets and vent lines are protected by hydrophobic 0.2 μm filters.

Seed Culture (200 Liters)

[0799] The 200 L seed bioreactor is equipped with 1 impeller for mixing, a dissolved oxygen probe, a temperature probe, a pH probe, aseptic sampling and additional systems. The first step of the cell cultivation process is the addition of INV-CDH medium into the bioreactor. After the medium temperature reaches 37 ± 0.5 °C, the DO and pH levels are stabilized by addition of N_2 and CO_2 to decrease dissolved oxygen concentration to 25 to 75% air saturation, and obtain a pH of 7.20 ± 0.2. The agitation rate is 35 rpm. The 25 L seed culture is transferred aseptically to the 200 L seed bioreactor containing 175 L sterile medium. During the eultivation process the temperature is maintained via plant steam and chilled glycol which regulate the temperature of the circulating jacket. The oxygen concentration is maintained via oxygen and nitrogen sparging and surface aeration, and pH is controlled by addition of CO_2 gas to lower the pH. The cultivation period is 4 days. The bioreactor air/gas inlet and vent lines are protected by hydrophobic 0.2 μm filters.

Production Culture (1600 Liters)

[0800] The production bioreactor is equipped with 2 impellers for mixing, a dissolved oxygen probe, a temperature probe, a pH probe, aseptic sampling and additional systems. 600 L of INV-CDH medium is aseptically transferred into the 1600 L production bioreactor. After the medium temperature reaches 37 ± 0.5°C, the DO and pH levels are stabilized by addition of N_2 and CO_2 to decrease dissolved oxygen concentration to 25 to 75% air saturation, and obtain a pH of 7.20 ± 0.2. The agitation rate is 17 rpm. The 200 L seed culture is aseptically transferred into the production bioreactor. During the cultivation process the temperature is maintained via plant steam and ehilled glycol whieh regulate the temperature of the circulating jacket, the oxygen concentration is maintained via oxygen and nitrohen sparging and surface aeration, and pH is controlled by addition of CO_2 gas to lower the pH. The bioreactor air/gas inlet and vent lines are protected by hydrophobic 0.2 μm filters. After 48 hours, 800 Liters of INV-CDH medium is

transferred into the production bioreactor in order to obtain the final volume. The culture is cultivated in the production bioreactor 43 additional days.

Recovery and Purification

Harvest of Cell Supernatant

[0801] Cell supernatant, (e.g., culture supernatant from NSO cells expressing antibodies of the invention) is harvested on day 5 or 6 post final feeding in the final production bioreactor. Cell culture broth temperature is cooled down to 15°C in the recovery vessel at the time of harvest and maintained at that temperature during the recovery. Centrifugation followed by depth filtration is used for cell removal and antibody recovery. The filtration proeess train consists of 0.1 µm nominal rated depth filter and 0.2 µm membrane fileters connected in series. A constant flow rate of 13 ± 1 L/min is maintained during the operation. The 0.2 µm filtered culture supernatant is collected in a process vessel, warned to 20°C and and transferred to purification. The purification process is conducted at 22 to 26°C.

Chromatography on rProtein A sepharose FF Column

[0802] The culture supernatant is loaded onto rProtein-A Sepharose FF column (affinity chromatography, Amersham Pharmacia) or equivalent column that is equilibrated in 50 mM Tris-HCl, 0.5 M NaCl, pH 7.5. The rProtein-A Sepharose FF column is washed with 0.05 M sodium citrate, 0.15 M sodium chloride, pH 5.2 and eluted with 0.05 M sodium citrate, 0.15 M sodium chloride, pH 3.2. The elution is monitored by ultraviolet (UV) absorbance at 280 nm. The elution peak is colleeted, and analyzed by A_{280} and SDS-PAGE.

Virus Inactivation

[0803] The eluate from the rProtein-A Sepharose FF column is adjusted with 1 M citric acid to pH 3.4 ± 0.2 and allowed to stand for 45-60 minutes for viral inactivation. The solution is then readjusted to pH 5.4 with 1 M Tris base. The pH adjusted material is 0.2 µm filtered and stored at 20°C up to 20 hours.

Chromatography on SP Sepharose FF Column

[0804] The inaetivated material from the rProtein-A Sepharose FF column is diluted with water for injection (WFI) to a conductivity of 7 mS, and loaded onto a SP Sepharose FF column (cation exchanger, Amersham-Pharmacia), or equivalent column equilibrated with 50 mM sodium acetate, 30mM sodium chloide, pH 5.4. The antibody is eluted from the SP column with 50 mM sodium acetate, 100 mM sodium chloride, pH 6.0. The elution is monitored by ultraviolet (UV) absorbance at 280 nm. The elution peak is collected and analyzed by A_{280} and SDS-PAGE.

Virus Removal Filtration, Diafiltration and Concentration

[0805] The eluate from the SP Sepharose FF column is filtered through a sequentially connected 0.2 μm filter and a virus removal filter (Pall DV50 Ultipor® VF Filter System). The DV50 filtrate is stored at 20°C up to 8 hours.

[0806] The DV50 filtrate is placed into a 30kD molecular weight cut-off membrane device (Millipore Pellicon) to concentrate to a target concentration of 35-40 mg/mL. The concentrated material is diafiltered against 10 mM sodium citrate, 1.9% glycine, 0.5% sucrose, pH 6.5. The diafiltered material is monitored by A_{280}. The diafiltered bulk is 0.2 μm filtered and stored at 20°C up to 8 hours.

Chromatography on Q Sepharose FF Column

[0807] The diafiltered antibody solution is passed over a Q Sepharose FF column (anion exchanger, Amersham-Pharmacia) or equivalent column equilibrated with 10 mM sodium citrate, 1.9% glycine, 0.5% sucrose, pH 6.5. The antibody is collected in the flow-through and monitored by A_{280}. The elution peak is collected and analyzed by A_{280}

Bulk Formulation, Filtration and Bulk Drug Substance Fill

[0808] Polysorbate 80 (1% stock solution in 10mM sodium citrate, 1.9% glycine and 0.5% sucrose) is pre-filtered through a 0.2 μm filter and added to the antibody solution to a final concentration of 0.01%. The purified antibody is aseptically filtered under a laminar flow hood through a 0.2 μm filter and filled into polypropylene containers.

Storage of Bulk Drug Substance

[0809] The bulk drug substanee is stored at 2-8 °C (short-term storage) or at or below –65 °C (long-term storage).

In Process Testing

[0810] In-process testing of bioreactor culture at harvest for each batch and in-process testing during the purification process are performed. The bioreactor is sampled aseptieally and the eulture is tested at various times throughout cultivation for cell density, viability and nutrient determination to ensure consistency of material being supplied for purification. The purification process is monitored at each step. Appearance is checked by vuisual inspection. The protein concentration is determined by Absorbance at 280nm. The pH of the material is checked. Purity is checked, for example, by SDS-PAGE and size exclusion chromatography. An ELISA may be performed to check the ability of the antibody to bind its antigen. The biological activity of the antibody is also monitored. Residual DNA content, Endotoxin levels, and the bioburden (the number of viable organisms present in the antibody preparation) are all monitored and kept at or below standard aeceptable levels. Additionally the oligosaccharide content may be analyzed; the peptide sequence of the antibody chains may also be analyzed using N–terminal sequencing and peptide mapping. Short and long-term studies of antibody stability may also be performed.

[0811] It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

[0812] The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in this application is incorporated in their entireties herein by reference. Further, the sequences disclosed herein are also disclosed in the Sequence Listings of U.S. Provisional Application 60/212,210 filed June 16, 2000 and U.S. Nonprovisional Application 09/880,748 filed June 15, 2001 the contents of which are herein incorporated in their entireties by reference.

[0813] Further, the Sequence Listing submitted herewith in both computer and paper forms are hereby incorporated by reference in their entireties. Additionally, the entire disclosure (including the specification, sequence listing, and drawings) of each of the following U.S. Provisional and Non-Provisional Patent Applications and International Patent Applications are herein incorporated by reference in their entireties: U.S. Provisional Application Serial Nos.: 60/331,469 filed November 16, 2001; 60/340,817 filed December 19, 2001; 60/212,210 filed June 16, 2000; 60/240,816 filed October 17 2000; 60/276,248 filed March 16, 2001; 60/277,379 filed March 21 2001; 60/293,499 filed May 25, 2001; and U.S. Nonprovisional Application Serial No. 09/880,748 filed June 15, 2001; and International Patent Application Serial No. PCT/US01/19110 filed June 15, 2001.

Table 1: scFvs that Immunospecifically Bind to BLyS

Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I003F12S	1	138 - 248	160 - 173	189 - 195	228 - 237	1 - 122	26 - 35	50 - 66	99 - 111	HDDDVLTGYYFES (SEQ ID NO: 2130)
I006D08	2	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYGMDV (SEQ ID NO: 2133)
I008A11	3	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 37	52 - 69	102 - 117	DRYDILTGYYYYGMDV (SEQ ID NO: 2129)
I017D10	4	148 - 255	169 - 179	195 - 201	234 - 244	1 - 132	26 - 35	50 - 66	99 - 121	VQMDSEYYDLLTGINVGPYYFDY (SEQ ID NO: 2132)
I022D01	5	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYYDILTGYSYYGMDV (SEQ ID NO: 2135)
I031F02	6	137 - 251	160 - 173	189 - 195	228 - 240	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
I050A12	7	140 - 250	164 - 174	190 - 196	229 - 239	1 - 124	26 - 35	50 - 66	99 - 113	APYDLLTHYFHYFDY (SEQ ID NO: 2134)
I051C04	8	145 - 256	168 - 181	197 - 203	236 - 245	1 - 129	26 - 35	50 - 66	99 - 118	AATTSQKHNKYAYYFYGMDV (SEQ ID NO: 2131)
I050B11	9	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I050B11-01	10	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQVWVA (SEQ ID NO: 2143)
I050B11-02	11	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQVWVA (SEQ ID NO: 2143)
I050B11-03	12	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTRYVFQYFDH (SEQ ID NO: 2144)
I050B11-04	13	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTGYVFQYFDH (SEQ ID NO: 2141)
I050B11-05	14	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTRYVFQVWVA (SEQ ID NO: 2142)
I050B11-06	15	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTGYVFQVWVA (SEQ ID NO: 2140)
I050B11-07	16	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTRYVFQYFDH (SEQ ID NO: 2144)
I050B11-08	17	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTGYVFQYFDH (SEQ ID NO: 2141)
I050B11-09	18	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTRYVFQVWVA (SEQ ID NO: 2142)
I050B11-10	19	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTRYVFQVWVA (SEQ ID NO: 2142)
I050B11-11	20	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTGYVFQVWVA (SEQ ID NO: 2140)
I050B11-12	21	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTGYVFQVWVA (SEQ ID NO: 2140)
I050B11-13	22	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I050B11-14	23	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I050B11-15	24	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQVWVA (SEQ ID NO: 2143)
I050B11-16	25	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQVWVA (SEQ ID NO: 2143)
I050B11-17	26	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTRYVFQYFDH (SEQ ID NO: 2144)
I050B11-18	27	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTRYVFQYFDH (SEQ ID NO: 2144)
I050B11-19	28	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTSYVFQYFDH (SEQ ID NO: 2139)
I050B11-20	29	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTSYVFQYFDH (SEQ ID NO: 2139)

I050B11-21	30	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTRYVFQYFDH (SEQ ID NO: 2138)
I050B11-22	31	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTRYVFQYFDH (SEQ ID NO: 2138)
I050B11-23	32	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTRYVFQYFDH (SEQ ID NO: 2138)
I050B11-24	33	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTSYVFQYFDH (SEQ ID NO: 2139)
I050B11-25	34	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTRYVFQYFDH (SEQ ID NO: 2144)
I050B11-26	35	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTSYVFQYFDH (SEQ ID NO: 2139)
I050B11-27	36	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTRYVFQYFDH (SEQ ID NO: 2138)
I050B11-28	37	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I093D03	38	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLGYYLS (SEQ ID NO: 2145)
I093D09	39	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I093G08	40	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQVWVA (SEQ ID NO: 2143)
I097D11	41	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTSYVFQYFDH (SEQ ID NO: 2139)
I101A04	42	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I101B01	43	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I102A02	44	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I102E01	45	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTRYVFQYFDH (SEQ ID NO: 2144)
I102G06	46	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTGYVFQYFDH (SEQ ID NO: 2141)
I087A07	47	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLPRVIP (SEQ ID NO: 2227)
I087A08	48	140 - 250	165 - 176	192 - 198	231 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PFYDTLTSYVCRPHF (SEQ ID NO: 2238)
I087A09	49	140 - 250	165 - 176	192 - 198	231 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PFYDTLTSYVRCPYV (SEQ ID NO: 2272)
I087B02	50	140 - 250	165 - 176	192 - 198	231 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PFYDTLTSYVFRPDL (SEQ ID NO: 2281)
I087B03	51	140 - 250	165 - 176	192 - 198	231 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PFYDTLTSYVKSMPT (SEQ ID NO: 2305)
I087B04	52	140 - 250	165 - 176	192 - 198	231 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PFYDTLTSYVPFLYC (SEQ ID NO: 2292)
I087B05	53	140 - 250	165 - 176	192 - 198	231 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PFYDTLTSYVPVPST (SEQ ID NO: 2270)
I087B06	54	140 - 250	165 - 176	192 - 198	231 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PFYDTLTSYVGIHGL (SEQ ID NO: 2282)
I087B08	55	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVPCSPPR (SEQ ID NO: 2261)
I087B09	56	140 - 250	165 - 176	192 - 198	231 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PFYDTLTSYVCYPPA (SEQ ID NO: 2240)
I087C02	57	140 - 250	165 - 176	192 - 198	231 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PFYDTLTSYVLPLLS (SEQ ID NO: 2224)
I087C05	58	140 - 250	165 - 176	192 - 198	231 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PFYDTLTSYVALYRL (SEQ ID NO: 2234)
I087C06	59	140 - 250	165 - 176	192 - 198	231 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PFYDTLTSYVRASFS (SEQ ID NO: 2271)
I087C07	60	140 - 250	165 - 176	192 - 198	231 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PFYDTLTSYVCTPVP (SEQ ID NO: 2319)
I087C08	61	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVWPSFFS (SEQ ID NO: 2277)
I087D01	62	140 - 250	165 - 176	192 - 198	231 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PFYDTLTSYVTPRGY (SEQ ID NO: 2275)
I087D02	63	140 - 250	165 - 176	192 - 198	231 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PFYDTLTSYVSSLLS (SEQ ID NO: 2213)
I087D03	64	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVPLLPLC (SEQ ID NO: 2263)
I087D05	65	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVPPPSFL (SEQ ID NO: 2266)

I087D07	66	140 - 250	165 - 176	192 - 198	231 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PFYDTLTSYVPTSTT (SEQ ID NO: 2269)
I087D09	67	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVISCSWA (SEQ ID NO: 2299)
I087E04	68	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVSALPPP (SEQ ID NO: 2274)
I087E05	69	140 - 250	165 - 176	192 - 198	231 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PFYDTLTSYVCRHLF (SEQ ID NO: 2236)
I087E10	70	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVVSFPSL (SEQ ID NO: 2307)
I087F02	71	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVMGVTPS (SEQ ID NO: 2322)
I087F04	72	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLFRPVL (SEQ ID NO: 2326)
I087F05	73	140 - 250	165 - 176	192 - 198	231 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PFYDTLTSYVPSVGG (SEQ ID NO: 2267)
I087F07	74	140 - 250	165 - 176	192 - 198	231 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PFYDTLTSYVPPTRH (SEQ ID NO: 2286)
I087F08	75	140 - 250	165 - 176	192 - 198	231 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PFYDTLTSYVLRSRD (SEQ ID NO: 2243)
I087F09	76	140 - 250	165 - 176	192 - 198	231 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PFYDTLTSYVPLLPP (SEQ ID NO: 2310)
I087G05	77	140 - 250	165 - 176	192 - 198	231 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PFYDTLTSYVLRCVL (SEQ ID NO: 2239)
I087G06	78	140 - 250	165 - 176	192 - 198	231 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PFYDTLTSYVHPSRS (SEQ ID NO: 2285)
I087G07	79	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLRLPPQ (SEQ ID NO: 2241)
I087G09	80	140 - 250	165 - 176	192 - 198	231 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PFYDTLTSYVGPYGT (SEQ ID NO: 2284)
I087G10	81	140 - 250	165 - 176	192 - 198	231 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PFYDTLTSYVTTPCT (SEQ ID NO: 2276)
I087H02	82	137 - 244	160 - 170	186 - 192	225 - 233	1 - 121	26 - 35	50 - 66	99 - 110	ASYLSTSSSLDN (SEQ ID NO: 2265)
I088A01	83	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I088A03	84	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVIPFLPL (SEQ ID NO: 2290)
I088A04	85	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLHIYPH (SEQ ID NO: 2335)
I088A08	86	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTNYVFEYYAS (SEQ ID NO: 2323)
I088A09	87	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVILYYLH (SEQ ID NO: 2295)
I088A10	88	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I088A11	89	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLMYFPH (SEQ ID NO: 2220)
I088A12	90	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLFFYPL (SEQ ID NO: 2325)
I088B01	91	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I088B02	92	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFDYYAS (SEQ ID NO: 2244)
I088B03	93	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVIPFLPL (SEQ ID NO: 2290)
I088B05	94	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I088B06	95	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFEYYSL (SEQ ID NO: 2324)
I088B07	96	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I088B08	97	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I088B09	98	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLEFYLL (SEQ ID NO: 2303)
I088B10	99	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I088B12	100	140 - 250	165 - 176	192 - 198	231 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PFYDTLTSYVLPLDS (SEQ ID NO: 2223)
I088C01	101	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLYFYPS (SEQ ID NO: 2317)

I088C03	102	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I088C09	103	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I088C12	104	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I088D01	105	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I088D03	106	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLHYYAL (SEQ ID NO: 2215)
I088D04	107	140 - 250	165 - 176	192 - 198	231 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PFYDTLTSYVLPPSV (SEQ ID NO: 2225)
I088D07	108	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I088D08	109	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I088D11	110	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I088E01	111	138 - 248	163 - 174	190 - 196	229 - 237	1 - 122	23 - 32	47 - 63	96 - 111	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I088E02	112	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLHYYLY (SEQ ID NO: 2216)
I088E03	113	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I088E04	114	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I088E08	115	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I088E10	116	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I088E11	117	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I088F07	118	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I088G02	119	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I088G03	120	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I088G07	121	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFHYYPL (SEQ ID NO: 2260)
I088G09	122	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFPVYYL (SEQ ID NO: 2264)
I088G10	123	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLHFIDH (SEQ ID NO: 2301)
I088H05	124	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I088H07	125	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I092A03	126	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I092A05	127	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFHYYDV (SEQ ID NO: 2258)
I092A06	128	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I092A08	129	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVHEFFSL (SEQ ID NO: 2283)
I092A10	130	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I092A11	131	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I092B01	132	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I092B02	133	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I092B04	134	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I092B05	135	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I092B10	136	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I092B12	137	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)

I092C01	138	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I092C02	139	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I092C07	140	140 - 250	165 - 176	192 - 198	231 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PFYDTLTSYVLALDL (SEQ ID NO: 2328)
I092C08	141	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFGYYSL (SEQ ID NO: 2254)
I092C12	142	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I092D01	143	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLKYYTD (SEQ ID NO: 2226)
I092D07	144	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I092D09	145	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVMHAYPL (SEQ ID NO: 2255)
I092D10	146	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFHYLPV (SEQ ID NO: 2256)
I092D11	147	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I092E01	148	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I092E03	149	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYAFQYFDH (SEQ ID NO: 2230)
I092E04	150	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFEYFSV (SEQ ID NO: 2248)
I092E07	151	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I092E10	152	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLFYYPL (SEQ ID NO: 2327)
I092E11	153	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I092F01	154	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I092F02	155	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I092F05	156	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I092F07	157	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I092F08	158	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I092F11	159	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I092F12	160	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLAYYPD (SEQ ID NO: 2306)
I092G01	161	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I092G05	162	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I092G10	163	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I092H01	164	137 - 244	160 - 170	186 - 192	225 - 233	1 - 121	26 - 35	50 - 66	99 - 110	ASYLSTSSSLDN (SEQ ID NO: 2265)
I093A06	165	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLPVYDH (SEQ ID NO: 2334)
I093A09	166	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFAH (SEQ ID NO: 2268)
I093A11	167	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I093A12	168	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I093B02	169	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I093B05	170	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVIFYYPT (SEQ ID NO: 2289)
I093B06	171	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I093B09	172	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLEVYHP (SEQ ID NO: 2318)
I093B12	173	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFAPLVT (SEQ ID NO: 2242)

I093C02	174	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLHAYAF (SEQ ID NO: 2332)
I093C03	175	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I093C05	176	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVILYYLH (SEQ ID NO: 2295)
I093D05	177	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFEFLPL (SEQ ID NO: 2245)
I093D08	178	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVRPFYAH (SEQ ID NO: 2273)
I093D10	179	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I093D12	180	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLHFYRV (SEQ ID NO: 2302)
I093E01	181	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I093E02	182	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVIQYFDH (SEQ ID NO: 2297)
I093E05	183	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVHEFFSL (SEQ ID NO: 2283)
I093E08	184	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVMQFFPT (SEQ ID NO: 2321)
I093E10	185	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLSFYPV (SEQ ID NO: 2246)
I093F01	186	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLYYYAF (SEQ ID NO: 2251)
I093F03	187	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I093F05	188	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I093F08	189	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I093F11	190	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLHFYPL (SEQ ID NO: 2333)
I093G07	191	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLQYYVL (SEQ ID NO: 2237)
I093G11	192	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I093G12	193	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I093H06	194	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I094A08	195	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDY (SEQ ID NO: 2280)
I094B07	196	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLPVWVS (SEQ ID NO: 2228)
I094B08	197	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I094B12	198	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I094C11	199	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I094C12	200	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I094D06	201	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVIEYYPV (SEQ ID NO: 2288)
I094D07	202	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I094D08	203	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLHYLPL (SEQ ID NO: 2314)
I094D09	204	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I094D10	205	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I094D11	206	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFHFYPV (SEQ ID NO: 2218)
I094E04	207	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I094E08	208	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLEAFSL (SEQ ID NO: 2311)
I094F04	209	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFGFYPF (SEQ ID NO: 2252)

I094F05	210	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I094F10	211	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PIYDTLTSYVFQYFDH (SEQ ID NO: 2278)
I094F11	212	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLWYYQD (SEQ ID NO: 2249)
I094F12	213	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVIPFYPL (SEQ ID NO: 2296)
I094G06	214	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I094G10	215	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I095A04	216	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I095A12	217	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLEYFPL (SEQ ID NO: 2320)
I095B04	218	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLEFFPA (SEQ ID NO: 2312)
I095B09	219	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVIEYLPL (SEQ ID NO: 2287)
I095B10	220	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLHYYSA (SEQ ID NO: 2217)
I095C02	221	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLFYYTA (SEQ ID NO: 2331)
I095C05	222	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLHYLPV (SEQ ID NO: 2337)
I095C07	223	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I095C08	224	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I095C09	225	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVMHYYPT (SEQ ID NO: 2259)
I095D01	226	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I095D02	227	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLQYFRY (SEQ ID NO: 2235)
I095D03	228	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLQVFDT (SEQ ID NO: 2233)
I095D05	229	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I095D09	230	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I095E01	231	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLDYYSS (SEQ ID NO: 2309)
I095E05	232	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDALTSYVFQYFDH (SEQ ID NO: 2221)
I095E12	233	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I095F06	234	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFPFYPH (SEQ ID NO: 2262)
I095F09	235	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVIGFYPV (SEQ ID NO: 2291)
I095G06	236	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I095G09	237	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVMDFYSV (SEQ ID NO: 2253)
I095G11	238	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I096A01	239	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I096A10	240	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLPFYAL (SEQ ID NO: 2222)
I096B01	241	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I096B03	242	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I096C01	243	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I096C06	244	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLPYLTH (SEQ ID NO: 2229)
I096C09	245	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)

I096D01	246	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I096D02	247	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I096D05	248	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I096D06	249	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I096D09	250	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I096E02	251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLGFYPV (SEQ ID NO: 2329)
I096E06	252	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLHYHTH (SEQ ID NO: 2336)
I096E11	253	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I096F02	254	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVIHFLPL (SEQ ID NO: 2330)
I096G01	255	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVIPFLPL (SEQ ID NO: 2290)
I096G02	256	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I096G05	257	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I096G07	258	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I096G09	259	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVMHYLPV (SEQ ID NO: 2257)
I096G12	260	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLEFFSH (SEQ ID NO: 2315)
I096H01	261	137 - 244	160 - 170	186 - 192	225 - 233	1 - 121	26 - 35	50 - 66	99 - 110	ASYLSTSSSLDN (SEQ ID NO: 2265)
I097A04	262	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVIHYLVT (SEQ ID NO: 2294)
I097A06	263	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLPYYTL (SEQ ID NO: 2231)
I097A09	264	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLHYYPI (SEQ ID NO: 2298)
I097B02	265	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLWFYPL (SEQ ID NO: 2247)
I097B09	266	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I097B10	267	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I097B11	268	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I097C05	269	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLHYYTH (SEQ ID NO: 2219)
I097C09	270	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLHYYAY (SEQ ID NO: 2316)
I097C11	271	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I097D05	272	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVIHFYSL (SEQ ID NO: 2293)
I097D06	273	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFGFFPH (SEQ ID NO: 2300)
I097E01	274	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I097E04	275	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I097E08	276	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I097E09	277	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I097F09	278	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I097G10	279	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFAH (SEQ ID NO: 2268)
I097H02	280	137 - 244	160 - 170	186 - 192	225 - 233	1 - 121	26 - 35	50 - 66	99 - 110	ASYLSTSSSLDN (SEQ ID NO: 2265)
I098A04	281	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)

I098A05	282	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I098B08	283	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLDFYSV (SEQ ID NO: 2308)
I098C01	284	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PIYDTLTSYVFQYFDH (SEQ ID NO: 2278)
I098C04	285	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLYYYAF (SEQ ID NO: 2251)
I098F11	286	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I098F12	287	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFFFYPF (SEQ ID NO: 2250)
I098G02	288	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I098G12	289	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I098H05	290	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I101A01	291	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I101B04	292	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I101B06	293	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVIPFLTH (SEQ ID NO: 2304)
I101D04	294	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLEFFPD (SEQ ID NO: 2313)
I101D07	295	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I101E09	296	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDR (SEQ ID NO: 2279)
I101E12	297	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I101G02	298	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I101G11	299	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I102C03	300	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I102E09	301	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I102F02	302	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I102G08	303	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I102G09	304	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLHYYAH (SEQ ID NO: 2214)
I106A09	305	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I106B02	306	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I106B06	307	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I106C07	308	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I106E05	309	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I106E12	310	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I106G01	311	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I106G03	312	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I109B06	313	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I109D12	314	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I109E12	315	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I109G06	316	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I109H04	317	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)

I110B03	318	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I112D09	319	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYGFQYFDH (SEQ ID NO: 2232)
I112F10	320	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I089F12	321	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHGLDS (SEQ ID NO: 2146)
I105E12	322	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHSFDL (SEQ ID NO: 2147)
I108D08	323	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPLAPLYP (SEQ ID NO: 2148)
I108E06	324	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHGLDV (SEQ ID NO: 2151)
I113E07	325	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHSLDL (SEQ ID NO: 2152)
I114G05	326	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHSFDL (SEQ ID NO: 2147)
I116A01	327	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHALSP (SEQ ID NO: 2149)
I116A09	328	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRYLLLFPHHSFDL (SEQ ID NO: 2150)
I116C11	329	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHSFDL (SEQ ID NO: 2147)
I085A01	330	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHDHLLF (SEQ ID NO: 2602)
I085A02	331	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSDPLGF (SEQ ID NO: 2639)
I085A03	332	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTHPLSF (SEQ ID NO: 2561)
I085A04	333	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPLAPLFF (SEQ ID NO: 2550)
I085A05	334	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSDPLSL (SEQ ID NO: 2659)
I085A06	335	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSAPLSF (SEQ ID NO: 2611)
I085A07	336	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPASPLSF (SEQ ID NO: 2390)
I085A09	337	138 - 248	162 - 172	188 - 194	227 - 237	1 - 122	26 - 35	50 - 66	99 - 111	SRDLLLFPNDALS (SEQ ID NO: 2632)
I085A10	338	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSAPLRF (SEQ ID NO: 2609)
I085A11	339	138 - 248	162 - 172	188 - 194	227 - 237	1 - 122	26 - 35	50 - 66	99 - 111	SRDLLLFPHDPLE (SEQ ID NO: 2363)
I085B01	340	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQSPLYP (SEQ ID NO: 2466)
I085B02	341	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHSSLVF (SEQ ID NO: 2392)
I085B03	342	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYDPLLF (SEQ ID NO: 2638)
I085B04	343	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHAPLYF (SEQ ID NO: 2589)
I085B05	344	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHAPLSP (SEQ ID NO: 2573)
I085B06	345	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPLSPLSF (SEQ ID NO: 2574)
I085B07	346	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPDFPMAP (SEQ ID NO: 2433)
I085B10	347	138 - 248	162 - 172	188 - 194	227 - 237	1 - 122	26 - 35	50 - 66	99 - 111	SRDLLLFPHSPLY (SEQ ID NO: 2470)
I085B12	348	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQDPLSP (SEQ ID NO: 2372)
I085C02	349	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPDDPLLS (SEQ ID NO: 2430)
I085C03	350	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHGPLLI (SEQ ID NO: 2400)
I085C05	351	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPGSPLLF (SEQ ID NO: 2491)
I085C06	352	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTAALSF (SEQ ID NO: 2341)
I085C07	353	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHTPLRF (SEQ ID NO: 2375)

I085C09	354	138 - 248	162 - 172	188 - 194	227 - 237	1 - 122	26 - 35	50 - 66	99 - 111	SRDLLLFPHSPLT (SEQ ID NO: 2468)
I085C10	355	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPFSPLLF (SEQ ID NO: 2471)
I085C12	356	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSHPLFF (SEQ ID NO: 2680)
I085D01	357	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRPLLLF (SEQ ID NO: 2548)
I085D02	358	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSQYLDF (SEQ ID NO: 2523)
I085D03	359	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSSPLLF (SEQ ID NO: 2713)
I085D04	360	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYFPLVF (SEQ ID NO: 2646)
I085D06	361	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPGSPLLD (SEQ ID NO: 2488)
I085D07	362	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQAPLLF (SEQ ID NO: 2694)
I085D08	363	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHSYLSP (SEQ ID NO: 2477)
I085D09	364	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQTPLFP (SEQ ID NO: 2467)
I085D10	365	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHSPLHP (SEQ ID NO: 2563)
I085D11	366	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHAPLAP (SEQ ID NO: 2510)
I085D12	367	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHTTLRF (SEQ ID NO: 2495)
I085E01	368	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYAVLHF (SEQ ID NO: 2620)
I085E02	369	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTSPLRL (SEQ ID NO: 2575)
I085E07	370	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSDALSF (SEQ ID NO: 2568)
I085E08	371	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPNAPLDP (SEQ ID NO: 2603)
I085E09	372	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHDPPRF (SEQ ID NO: 2628)
I085E10	373	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSEPLWP (SEQ ID NO: 2668)
I085E11	374	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSSPLSN (SEQ ID NO: 2716)
I085E12	375	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHLPLTP (SEQ ID NO: 2431)
I085F01	376	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRSPLLF (SEQ ID NO: 2551)
I085F02	377	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTSPLQL (SEQ ID NO: 2376)
I085F03	378	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYTPLLF (SEQ ID NO: 2682)
I085F04	379	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSSPLAF (SEQ ID NO: 2707)
I085F05	380	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHDPLYF (SEQ ID NO: 2706)
I085F06	381	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSAHLLF (SEQ ID NO: 2586)
I085F07	382	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPAGPLRF (SEQ ID NO: 2410)
I085F09	383	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPDHAFFV (SEQ ID NO: 2439)
I085F10	384	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSDSGFA (SEQ ID NO: 2662)
I085F11	385	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSSYLEF (SEQ ID NO: 2339)
I085F12	386	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRDPLII (SEQ ID NO: 2558)
I085G01	387	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSAPLHP (SEQ ID NO: 2605)
I085G02	388	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPNAPLLL (SEQ ID NO: 2613)
I085G03	389	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPAAPLLF (SEQ ID NO: 2403)

I085G04	390	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSAPLDP (SEQ ID NO: 2601)
I085G07	391	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPNAVLDI (SEQ ID NO: 2629)
I085G08	392	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSEPLFF (SEQ ID NO: 2664)
I085G09	393	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSSVLWP (SEQ ID NO: 2338)
I085G10	394	138 - 248	162 - 172	188 - 194	227 - 237	1 - 122	26 - 35	50 - 66	99 - 111	SRDLLLFPHAPLQ (SEQ ID NO: 2554)
I085G11	395	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPDSPLAP (SEQ ID NO: 2445)
I085G12	396	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSSPLHP (SEQ ID NO: 2576)
I085H10	397	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYYDILTGYSYYGMDV (SEQ ID NO: 2135)
I086A03	398	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSMPLTF (SEQ ID NO: 2695)
I086A04	399	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHSILHP (SEQ ID NO: 2438)
I086A05	400	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHAPLSH (SEQ ID NO: 2569)
I086A07	401	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPDAALRF (SEQ ID NO: 2421)
I086A09	402	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSSHLSF (SEQ ID NO: 2704)
I086A10	403	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSAPLSS (SEQ ID NO: 2624)
I086A11	404	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHAPLTP (SEQ ID NO: 2577)
I086A12	405	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYDPLHS (SEQ ID NO: 2635)
I086B02	406	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHFPLHP (SEQ ID NO: 2348)
I086B03	407	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPAHPLLF (SEQ ID NO: 2412)
I086B05	408	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPFEPLII (SEQ ID NO: 2457)
I086B06	409	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPASPLNP (SEQ ID NO: 2364)
I086B07	410	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSSPLYF (SEQ ID NO: 2720)
I086B09	411	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTSPLSF (SEQ ID NO: 2579)
I086B10	412	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPDDGLSS (SEQ ID NO: 2428)
I086B11	413	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPISPLCF (SEQ ID NO: 2530)
I086C03	414	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTAPLYG (SEQ ID NO: 2535)
I086C05	415	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHSLFF (SEQ ID NO: 2427)
I086C07	416	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQGPLRF (SEQ ID NO: 2440)
I086C08	417	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPAAPLAF (SEQ ID NO: 2401)
I086C09	418	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHLPLLF (SEQ ID NO: 2350)
I086C10	419	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTFPLIF (SEQ ID NO: 2541)
I086C11	420	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPDDPLSF (SEQ ID NO: 2432)
I086C12	421	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTDSLLF (SEQ ID NO: 2622)
I086D01	422	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSAPLTP (SEQ ID NO: 2630)
I086D04	423	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRYLLLFPYAPLYD (SEQ ID NO: 2697)
I086D05	424	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHSPLSF (SEQ ID NO: 2461)
I086D06	425	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTAPLDL (SEQ ID NO: 2379)

I086D07	426	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHTHLTF (SEQ ID NO: 2365)
I086D08	427	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHSSLDF (SEQ ID NO: 2473)
I086D09	428	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPNHPMFP (SEQ ID NO: 2665)
I086D10	429	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPLSSLEF (SEQ ID NO: 2587)
I086D11	430	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPNAPLHP (SEQ ID NO: 2610)
I086D12	431	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRAHLRF (SEQ ID NO: 2469)
I086E02	432	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYDPLHF (SEQ ID NO: 2621)
I086E03	433	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHDALQS (SEQ ID NO: 2598)
I086E05	434	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRTPLTF (SEQ ID NO: 2567)
I086E07	435	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPAAHLSF (SEQ ID NO: 2398)
I086E08	436	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRAPLLF (SEQ ID NO: 2490)
I086E09	437	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPFSPLAP (SEQ ID NO: 2464)
I086E10	438	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRAPLDF (SEQ ID NO: 2367)
I086E12	439	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTAPLRF (SEQ ID NO: 2522)
I086F02	440	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSSPLRI (SEQ ID NO: 2714)
I086F05	441	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTEPLQF (SEQ ID NO: 2540)
I086F08	442	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSDPLSA (SEQ ID NO: 2643)
I086F09	443	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYNPPIF (SEQ ID NO: 2653)
I086F11	444	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHTPLLF (SEQ ID NO: 2489)
I086G03	445	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHAPLDL (SEQ ID NO: 2513)
I086G04	446	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPFDPLLI (SEQ ID NO: 2454)
I086G05	447	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTDALRI (SEQ ID NO: 2537)
I086G06	448	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPAAPLTP (SEQ ID NO: 2407)
I086G07	449	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPEGPLLF (SEQ ID NO: 2448)
I086G09	450	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYAPLSF (SEQ ID NO: 2385)
I086G10	451	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPADSLSF (SEQ ID NO: 2391)
I086H05	452	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYSPLTH (SEQ ID NO: 2679)
I089A01	453	138 - 248	162 - 172	188 - 194	227 - 237	1 - 122	26 - 35	50 - 66	99 - 111	SRDLLLFPHDPLI (SEQ ID NO: 2612)
I089A03	454	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPLTPLLI (SEQ ID NO: 2590)
I089A06	455	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHTPLHF (SEQ ID NO: 2485)
I089A07	456	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTDALYF (SEQ ID NO: 2539)
I089A08	457	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYTPLLF (SEQ ID NO: 2682)
I089A10	458	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHQPLTF (SEQ ID NO: 2436)
I089A11	459	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRTYLDF (SEQ ID NO: 2572)
I089B01	460	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHSPLHS (SEQ ID NO: 2450)
I089B02	461	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHSFDL (SEQ ID NO: 2147)

I089B03	462	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTSPLQP (SEQ ID NO: 2528)
I089B04	463	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTHPLLF (SEQ ID NO: 2556)
I089B05	464	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSSPLIF (SEQ ID NO: 2712)
I089B06	465	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPMAPLSP (SEQ ID NO: 2596)
I089B07	466	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYSGLDA (SEQ ID NO: 2374)
I089B08	467	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPAAPLSP (SEQ ID NO: 2405)
I089B09	468	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPKSPILF (SEQ ID NO: 2384)
I089B10	469	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTSPLFF (SEQ ID NO: 2571)
I089B11	470	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPNSPLFP (SEQ ID NO: 2388)
I089C01	471	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYGMDV (SEQ ID NO: 2133)
I089C02	472	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRSPLLF (SEQ ID NO: 2551)
I089C03	473	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYHPLLF (SEQ ID NO: 2532)
I089C05	474	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSSALRF (SEQ ID NO: 2722)
I089C06	475	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSPYLSF (SEQ ID NO: 2701)
I089C07	476	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQAPLFD (SEQ ID NO: 2683)
I089C09	477	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHAPFTF (SEQ ID NO: 2507)
I089D01	478	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHAPLVL (SEQ ID NO: 2581)
I089D02	479	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYGMDV (SEQ ID NO: 2133)
I089D03	480	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYPLLF (SEQ ID NO: 2344)
I089D04	481	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSSPLSP (SEQ ID NO: 2717)
I089D05	482	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHAPLFT (SEQ ID NO: 2546)
I089D07	483	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPNDPLLI (SEQ ID NO: 2634)
I089D08	484	138 - 248	162 - 172	188 - 194	227 - 237	1 - 122	26 - 35	50 - 66	99 - 111	SRDLLLFPHAPLQ (SEQ ID NO: 2554)
I089D09	485	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSHAFHE (SEQ ID NO: 2677)
I089D11	486	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPNHPLYP (SEQ ID NO: 2663)
I089E01	487	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYSPLFP (SEQ ID NO: 2657)
I089E02	488	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQDPLHP (SEQ ID NO: 2346)
I089E03	489	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPDAPLFP (SEQ ID NO: 2423)
I089E04	490	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHSPLLI (SEQ ID NO: 2453)
I089E06	491	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPGSPLLF (SEQ ID NO: 2491)
I089E09	492	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSSPLTF (SEQ ID NO: 2718)
I089E10	493	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTQPLSF (SEQ ID NO: 2566)
I089E11	494	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPLSPLWP (SEQ ID NO: 2578)
I089F01	495	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTFPLLF (SEQ ID NO: 2380)
I089F03	496	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHDPLLL (SEQ ID NO: 2580)
I089F04	497	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYSPLLF (SEQ ID NO: 2670)

I089F05	498	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHSPLRI (SEQ ID NO: 2459)
I089F06	499	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRAPLLF (SEQ ID NO: 2490)
I089F08	500	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRTPLTF (SEQ ID NO: 2567)
I089F09	501	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPLAPLSF (SEQ ID NO: 2555)
I089F10	502	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPNQPLSF (SEQ ID NO: 2667)
I089F11	503	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPLEPMHF (SEQ ID NO: 2565)
I089G01	504	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSAPLTF (SEQ ID NO: 2626)
I089G02	505	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSHPLLF (SEQ ID NO: 2687)
I089G03	506	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRTPLVF (SEQ ID NO: 2721)
I089G05	507	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPGSPLTF (SEQ ID NO: 2389)
I089G06	508	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTAPLLF (SEQ ID NO: 2514)
I089G07	509	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSAPLDF (SEQ ID NO: 2597)
I089G08	510	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSHPLSF (SEQ ID NO: 2688)
I089G11	511	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSFPLLF (SEQ ID NO: 2671)
I089H10	512	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYYDILTGYSYYGMDV (SEQ ID NO: 2135)
I090A02	513	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPAKPLLF (SEQ ID NO: 2416)
I090A03	514	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPNSTLSF (SEQ ID NO: 2678)
I090A04	515	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPDAPLTP (SEQ ID NO: 2426)
I090A05	516	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHEPLLI (SEQ ID NO: 2648)
I090A06	517	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTYPLSF (SEQ ID NO: 2600)
I090A07	518	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTEPLVL (SEQ ID NO: 2479)
I090A08	519	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTYPLHF (SEQ ID NO: 2584)
I090B01	520	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHDPLTF (SEQ ID NO: 2627)
I090B03	521	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQAPLTN (SEQ ID NO: 2705)
I090B04	522	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHAPLEA (SEQ ID NO: 2520)
I090B05	523	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPDHPLLF (SEQ ID NO: 2442)
I090B06	524	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRAPLSF (SEQ ID NO: 2496)
I090B08	525	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRGPLRF (SEQ ID NO: 2542)
I090B11	526	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPFTPLTF (SEQ ID NO: 2474)
I090B12	527	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQHPLSP (SEQ ID NO: 2452)
I090C01	528	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSAPIVF (SEQ ID NO: 2591)
I090C02	529	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQAPLTF (SEQ ID NO: 2702)
I090C03	530	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRAPLRF (SEQ ID NO: 2493)
I090C05	531	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRTPLTF (SEQ ID NO: 2567)
I090C06	532	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHAPLDF (SEQ ID NO: 2538)
I090C07	533	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHAGFDS (SEQ ID NO: 2498)

I090C08	534	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYSPLSF (SEQ ID NO: 2676)
I090C10	535	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPGRPLTF (SEQ ID NO: 2358)
I090D02	536	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPAEHLLF (SEQ ID NO: 2408)
I090D03	537	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTAPLHP (SEQ ID NO: 2351)
I090D04	538	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHEPLTA (SEQ ID NO: 2654)
I090D05	539	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHAPLFE (SEQ ID NO: 2529)
I090D06	540	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRAPLDF (SEQ ID NO: 2367)
I090D07	541	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPFGTLRF (SEQ ID NO: 2462)
I090D08	542	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSSPLVF (SEQ ID NO: 2723)
I090D09	543	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRDPLAF (SEQ ID NO: 2505)
I090D12	544	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTSPLSF (SEQ ID NO: 2579)
I090E04	545	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHAPLLL (SEQ ID NO: 2552)
I090E05	546	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSAPISF (SEQ ID NO: 2588)
I090E06	547	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQGPLSF (SEQ ID NO: 2443)
I090E07	548	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPGSPLHP (SEQ ID NO: 2484)
I090E09	549	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSDPLSF (SEQ ID NO: 2647)
I090E11	550	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHDGLAP (SEQ ID NO: 2700)
I090E12	551	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTSPLTF (SEQ ID NO: 2582)
I090F01	552	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPNGPLHP (SEQ ID NO: 2649)
I090F02	553	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQAPLSF (SEQ ID NO: 2696)
I090F03	554	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTAPLSF (SEQ ID NO: 2526)
I090F04	555	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPFFPLQF (SEQ ID NO: 2460)
I090F05	556	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPLDPLHF (SEQ ID NO: 2359)
I090F06	557	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSEPLQL (SEQ ID NO: 2666)
I090F07	558	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPFAPLRF (SEQ ID NO: 2451)
I090F08	559	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPLHPLIF (SEQ ID NO: 2570)
I090F09	560	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYPLLF (SEQ ID NO: 2344)
I090F10	561	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRDPLRI (SEQ ID NO: 2527)
I090F11	562	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSNPLTF (SEQ ID NO: 2698)
I090G01	563	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTAPLEI (SEQ ID NO: 2347)
I090G02	564	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRDPLQF (SEQ ID NO: 2395)
I090G04	565	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHEPLAF (SEQ ID NO: 2633)
I090G05	566	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRAPLAF (SEQ ID NO: 2472)
I090G06	567	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYSPLAF (SEQ ID NO: 2656)
I090G07	568	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHTPLDS (SEQ ID NO: 2480)
I090G08	569	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHTPLTF (SEQ ID NO: 2492)

I090G09	570	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSEPLRI (SEQ ID NO: 2356)
I090G10	571	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTAPLDF (SEQ ID NO: 2343)
I090G12	572	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPNRGLDL (SEQ ID NO: 2669)
I091A02	573	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYDPLFM (SEQ ID NO: 2724)
I091A03	574	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHAPLYP (SEQ ID NO: 2592)
I091A06	575	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSAPLAF (SEQ ID NO: 2594)
I091A11	576	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHSPITF (SEQ ID NO: 2441)
I091B01	577	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRYPLFF (SEQ ID NO: 2585)
I091B02	578	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYAPLDF (SEQ ID NO: 2361)
I091B04	579	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRDPLQF (SEQ ID NO: 2395)
I091B05	580	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHAPLEL (SEQ ID NO: 2475)
I091B07	581	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSAPLTF (SEQ ID NO: 2626)
I091B10	582	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTAPLAF (SEQ ID NO: 2342)
I091B11	583	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHSPLDF (SEQ ID NO: 2444)
I091B12	584	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSHPLTF (SEQ ID NO: 2690)
I091C02	585	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPAHPLVI (SEQ ID NO: 2414)
I091C03	586	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQAPLYP (SEQ ID NO: 2378)
I091C04	587	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTAPLTF (SEQ ID NO: 2531)
I091C05	588	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTTPLHF (SEQ ID NO: 2583)
I091C06	589	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYPLLF (SEQ ID NO: 2344)
I091C09	590	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHPLSF (SEQ ID NO: 2415)
I091C11	591	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYHSYDI (SEQ ID NO: 2650)
I091C12	592	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYATLSF (SEQ ID NO: 2618)
I091D01	593	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPNSPLAP (SEQ ID NO: 2672)
I091D02	594	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYSPLQP (SEQ ID NO: 2673)
I091D04	595	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQGPLSF (SEQ ID NO: 2443)
I091D05	596	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHDPLAP (SEQ ID NO: 2606)
I091D06	597	138 - 248	162 - 172	188 - 194	227 - 237	1 - 122	26 - 35	50 - 66	99 - 111	SRDLLLFPHSPLL (SEQ ID NO: 2456)
I091D07	598	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPNGALRF (SEQ ID NO: 2645)
I091D09	599	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYSPLRF (SEQ ID NO: 2719)
I091E01	600	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPDAPLHP (SEQ ID NO: 2425)
I091E02	601	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQAPLFP (SEQ ID NO: 2689)
I091E03	602	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSAPLWP (SEQ ID NO: 2352)
I091E04	603	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPKSPLAF (SEQ ID NO: 2547)
I091E06	604	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSSPLHP (SEQ ID NO: 2576)
I091E07	605	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPNHPLTF (SEQ ID NO: 2661)

I091E08	606	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPNAPLDS (SEQ ID NO: 2607)
I091E09	607	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYAPLDF (SEQ ID NO: 2361)
I091E10	608	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSSPLEF (SEQ ID NO: 2711)
I091F01	609	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRAPLFF (SEQ ID NO: 2486)
I091F03	610	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPMAPLVG (SEQ ID NO: 2599)
I091F05	611	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPLAPLHP (SEQ ID NO: 2553)
I091F06	612	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHDPLGF (SEQ ID NO: 2353)
I091F07	613	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYGMDV (SEQ ID NO: 2133)
I091F08	614	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQSPLLF (SEQ ID NO: 2458)
I091F09	615	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHEHLSF (SEQ ID NO: 2354)
I091F10	616	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHSPLDF (SEQ ID NO: 2444)
I091F11	617	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHSPLSP (SEQ ID NO: 2549)
I091F12	618	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYGMDV (SEQ ID NO: 2133)
I091G01	619	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPNAALYP (SEQ ID NO: 2386)
I091G03	620	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPNDPLFG (SEQ ID NO: 2355)
I091G04	621	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPGAPLSP (SEQ ID NO: 2478)
I091G05	622	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	ARDLLLFPAAPLWP (SEQ ID NO: 2397)
I091G06	623	138 - 248	162 - 172	188 - 194	227 - 237	1 - 122	26 - 35	50 - 66	99 - 111	SRDLLLFPNDPLR (SEQ ID NO: 2637)
I091G07	624	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTAPLDP (SEQ ID NO: 2345)
I091G09	625	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTAPLFP (SEQ ID NO: 2349)
I091G10	626	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSDPLVF (SEQ ID NO: 2660)
I091G11	627	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPGSPLTF (SEQ ID NO: 2389)
I091G12	628	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYSHLEF (SEQ ID NO: 2655)
I104A01	629	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQSPLHP (SEQ ID NO: 2455)
I104A07	630	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQAPLFP (SEQ ID NO: 2689)
I104A08	631	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYAPLTF (SEQ ID NO: 2617)
I104A09	632	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQNPLHP (SEQ ID NO: 2506)
I104A10	633	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHEPLCF (SEQ ID NO: 2636)
I104A11	634	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSAPLSF (SEQ ID NO: 2611)
I104A12	635	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPMAPLRF (SEQ ID NO: 2593)
I104B02	636	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRSPLSF (SEQ ID NO: 2557)
I104B04	637	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSAPLYP (SEQ ID NO: 2387)
I104B09	638	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRDPLQF (SEQ ID NO: 2395)
I104B11	639	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTAPLTF (SEQ ID NO: 2531)
I104C01	640	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYSPLYP (SEQ ID NO: 2710)
I104C04	641	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPASPLIF (SEQ ID NO: 2417)

I104C05	642	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRHPLLF (SEQ ID NO: 2543)
I104C06	643	138 - 248	162 - 172	188 - 194	227 - 237	1 - 122	26 - 35	50 - 66	99 - 111	SRDLLLFPHAPLE (SEQ ID NO: 2524)
I104C07	644	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHAPLHP (SEQ ID NO: 2370)
I104C09	645	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHFPLIF (SEQ ID NO: 2399)
I104C11	646	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHEPLIF (SEQ ID NO: 2644)
I104D01	647	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPNHAFDL (SEQ ID NO: 2652)
I104D02	648	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHTILYP (SEQ ID NO: 2497)
I104D03	649	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPDWPLYP (SEQ ID NO: 2483)
I104D04	650	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYPLFL (SEQ ID NO: 2511)
I104D07	651	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQAPLHP (SEQ ID NO: 2691)
I104D08	652	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHAPMDP (SEQ ID NO: 2595)
I104D09	653	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRAPLTF (SEQ ID NO: 2500)
I104E01	654	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRATLEF (SEQ ID NO: 2502)
I104E02	655	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHSPLFP (SEQ ID NO: 2447)
I104E03	656	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPNDPLVL (SEQ ID NO: 2641)
I104E05	657	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHDPLYI (SEQ ID NO: 2463)
I104E11	658	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYAPLSF (SEQ ID NO: 2385)
I104E12	659	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPASPLNP (SEQ ID NO: 2364)
I104F02	660	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHDPLSP (SEQ ID NO: 2616)
I104F03	661	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRDPLRF (SEQ ID NO: 2360)
I104F04	662	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPGDPLDF (SEQ ID NO: 2481)
I104F05	663	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHGPLTF (SEQ ID NO: 2402)
I104F06	664	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHAPLSP (SEQ ID NO: 2573)
I104F07	665	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSSPLIL (SEQ ID NO: 2465)
I104F10	666	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPNSPLSP (SEQ ID NO: 2362)
I104F11	667	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQDPLVF (SEQ ID NO: 2708)
I104F12	668	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPKAPLVF (SEQ ID NO: 2544)
I104G04	669	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHAPLRF (SEQ ID NO: 2559)
I104G05	670	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRAPLAP (SEQ ID NO: 2476)
I104G09	671	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTAPLNF (SEQ ID NO: 2518)
I104G11	672	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRHLLLFPQGPLSF (SEQ ID NO: 2482)
I105A02	673	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHLPLNP (SEQ ID NO: 2494)
I105A03	674	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHSFDL (SEQ ID NO: 2147)
I105A04	675	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPGAPLAP (SEQ ID NO: 2487)
I105A08	676	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQAPLYP (SEQ ID NO: 2378)
I105A09	677	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRSPLSF (SEQ ID NO: 2557)

I105A11	678	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSHSFDI (SEQ ID NO: 2692)
I105B04	679	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYSPLHP (SEQ ID NO: 2658)
I105B05	680	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYSPLSF (SEQ ID NO: 2676)
I105B07	681	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHSFDL (SEQ ID NO: 2147)
I105B08	682	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHSFDL (SEQ ID NO: 2147)
I105B10	683	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPASPLNP (SEQ ID NO: 2364)
I105B11	684	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHEPLSP (SEQ ID NO: 2651)
I105B12	685	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPLDPLII (SEQ ID NO: 2560)
I105C02	686	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRAPLAF (SEQ ID NO: 2472)
I105C03	687	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSSPLSF (SEQ ID NO: 2715)
I105C05	688	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYGMDV (SEQ ID NO: 2133)
I105C06	689	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRAPLDF (SEQ ID NO: 2367)
I105C08	690	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRSPLTF (SEQ ID NO: 2562)
I105C12	691	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQHGFDA (SEQ ID NO: 2446)
I105D04	692	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRDPLRF (SEQ ID NO: 2360)
I105D06	693	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRDPLSF (SEQ ID NO: 2368)
I105D08	694	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYAPLAF (SEQ ID NO: 2608)
I105D09	695	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHAAFDV (SEQ ID NO: 2619)
I105D10	696	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHEPLFP (SEQ ID NO: 2640)
I105D11	697	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRSALTF (SEQ ID NO: 2519)
I105E01	698	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHSFDS (SEQ ID NO: 2422)
I105E06	699	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYGMDV (SEQ ID NO: 2133)
I105E11	700	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPNSPLHP (SEQ ID NO: 2675)
I105F03	701	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHPLDS (SEQ ID NO: 2409)
I105F06	702	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQAPLHP (SEQ ID NO: 2691)
I105F07	703	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSWPLTF (SEQ ID NO: 2340)
I105F09	704	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYPLLF (SEQ ID NO: 2344)
I105F12	705	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPTYPLVF (SEQ ID NO: 2604)
I105G03	706	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHAPLHP (SEQ ID NO: 2370)
I105G08	707	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPKHPLVF (SEQ ID NO: 2366)
I105G09	708	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPASPLNP (SEQ ID NO: 2364)
I105G10	709	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHSFDA (SEQ ID NO: 2419)
I105G11	710	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHDPLLF (SEQ ID NO: 2614)
I107A01	711	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRHPLVF (SEQ ID NO: 2545)
I107A03	712	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRAPLYP (SEQ ID NO: 2501)
I107A06	713	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHAPLDP (SEQ ID NO: 2369)

I107A07	714	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPNAPLSP (SEQ ID NO: 2371)
I107A09	715	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQAPLSP (SEQ ID NO: 2699)
I107A12	716	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHAPLSF (SEQ ID NO: 2564)
I107B02	717	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHAPLFP (SEQ ID NO: 2533)
I107B04	718	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPASPLTF (SEQ ID NO: 2420)
I107B05	719	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYGMDV (SEQ ID NO: 2133)
I107C01	720	137 - 247	161 - 171	187 - 193	226 - 236	1 - 121	24 - 33	48 - 64	97 - 110	SRDLLLFPHYPLLF (SEQ ID NO: 2344)
I107C02	721	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYGMYV (SEQ ID NO: 2504)
I107C04	722	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYPLHP (SEQ ID NO: 2357)
I107C06	723	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHAPLAP (SEQ ID NO: 2510)
I107C08	724	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQAPLEP (SEQ ID NO: 2681)
I107C10	725	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSHAFDL (SEQ ID NO: 2674)
I107D01	726	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYAPLDF (SEQ ID NO: 2361)
I107D04	727	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPNAPLSF (SEQ ID NO: 2625)
I107D07	728	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSHSFDV (SEQ ID NO: 2693)
I107D12	729	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHSFDT (SEQ ID NO: 2424)
I107E01	730	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPMLGLDL (SEQ ID NO: 2499)
I107E05	731	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRAPLDF (SEQ ID NO: 2367)
I107E07	732	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRSPLLF (SEQ ID NO: 2551)
I107E09	733	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPKAPLTF (SEQ ID NO: 2382)
I107F01	734	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSAPLSP (SEQ ID NO: 2623)
I107F05	735	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHAPLAP (SEQ ID NO: 2510)
I107F09	736	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSAPLAP (SEQ ID NO: 2394)
I107F10	737	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRTPLLF (SEQ ID NO: 2373)
I107G01	738	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPNAPLSP (SEQ ID NO: 2371)
I107G05	739	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSAPLYP (SEQ ID NO: 2387)
I107H02	740	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHSFDL (SEQ ID NO: 2147)
I107H06	741	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRAPLSF (SEQ ID NO: 2496)
I107H09	742	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYPLEM (SEQ ID NO: 2536)
I107H10	743	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHAPLAP (SEQ ID NO: 2510)
I108A12	744	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHSFDL (SEQ ID NO: 2147)
I108B03	745	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRDPLLF (SEQ ID NO: 2515)
I108B04	746	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPLSPLVP (SEQ ID NO: 2396)
I108C09	747	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHDPLGF (SEQ ID NO: 2353)
I108C11	748	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHSLLF (SEQ ID NO: 2429)
I108D10	749	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPASPLNP (SEQ ID NO: 2364)

I108D11	750	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPASPLNP (SEQ ID NO: 2364)
I108D12	751	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSAPLNP (SEQ ID NO: 2709)
I108E01	752	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHSFDL (SEQ ID NO: 2147)
I108E03	753	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPKHPLRF (SEQ ID NO: 2393)
I108E05	754	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHAPLFP (SEQ ID NO: 2533)
I108E07	755	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHAPLDP (SEQ ID NO: 2369)
I108E08	756	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYPLLF (SEQ ID NO: 2344)
I108E09	757	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSAPLSP (SEQ ID NO: 2623)
I108E10	758	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRDPLDL (SEQ ID NO: 2509)
I108E11	759	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRDPLEF (SEQ ID NO: 2516)
I108F10	760	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPNAPLSP (SEQ ID NO: 2371)
I108F12	761	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYPFDA (SEQ ID NO: 2508)
I108G01	762	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRDPLRF (SEQ ID NO: 2360)
I108G02	763	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPDAPLAP (SEQ ID NO: 2381)
I108G07	764	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRAPLAP (SEQ ID NO: 2476)
I108G10	765	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHSLLF (SEQ ID NO: 2429)
I108G11	766	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHPLTF (SEQ ID NO: 2377)
I108G12	767	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHPLTF (SEQ ID NO: 2377)
I108H01	768	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRDPLHF (SEQ ID NO: 2512)
I108H02	769	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPNAPLNP (SEQ ID NO: 2615)
I108H06	770	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHSFDL (SEQ ID NO: 2147)
I108H08	771	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPASPLNP (SEQ ID NO: 2364)
I111A06	772	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQAPLHP (SEQ ID NO: 2691)
I111B12	773	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHSFDL (SEQ ID NO: 2147)
I111C01	774	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQHGLDL (SEQ ID NO: 2449)
I111D06	775	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRDPLLF (SEQ ID NO: 2515)
I111E04	776	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHSFDL (SEQ ID NO: 2147)
I111E10	777	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQAPLHP (SEQ ID NO: 2691)
I111E11	778	139 - 250	163 - 173	189 - 195	229 - 239	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYPLLF (SEQ ID NO: 2344)
I111E12	779	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRYLLLFPHHSFDL (SEQ ID NO: 2150)
I111F07	780	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRAPLYP (SEQ ID NO: 2501)
I111G02	781	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPKAPLDF (SEQ ID NO: 2534)
I111H10	782	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRYLLLFPQHGFDA (SEQ ID NO: 2703)
I113A04	783	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSAPLWP (SEQ ID NO: 2352)
I113A12	784	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQEPLAP (SEQ ID NO: 2434)
I113B06	785	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHPLEP (SEQ ID NO: 2411)

I113C06	786	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHGFDA (SEQ ID NO: 2406)
I113G04	787	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYPLLF (SEQ ID NO: 2344)
I113G05	788	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYSLLL (SEQ ID NO: 2517)
I113G10	789	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHPLQF (SEQ ID NO: 2413)
I113G11	790	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYPLLF (SEQ ID NO: 2344)
I113H06	791	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYPLLF (SEQ ID NO: 2344)
I113H07	792	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHSFDL (SEQ ID NO: 2147)
I113H09	793	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYTLLF (SEQ ID NO: 2525)
I114C04	794	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHGFDA (SEQ ID NO: 2406)
I114C12	795	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQAPLHP (SEQ ID NO: 2691)
I114D04	796	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYGMDV (SEQ ID NO: 2133)
I114D06	797	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHSFDL (SEQ ID NO: 2147)
I114D10	798	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYSLVL (SEQ ID NO: 2521)
I114E01	799	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQEPLSP (SEQ ID NO: 2435)
I114E02	800	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQESFSL (SEQ ID NO: 2437)
I114E03	801	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPKAPLTF (SEQ ID NO: 2382)
I114E11	802	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHDSFFL (SEQ ID NO: 2383)
I114H01	803	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHSFDL (SEQ ID NO: 2147)
I114H06	804	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHALDV (SEQ ID NO: 2404)
I114H09	805	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHSFDL (SEQ ID NO: 2147)
I115A02	806	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRYLLLFPDHSFDL (SEQ ID NO: 2684)
I115A07	807	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYPLLF (SEQ ID NO: 2344)
I115B10	808	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHSFDL (SEQ ID NO: 2147)
I115C05	809	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRAPLYP (SEQ ID NO: 2501)
I115C06	810	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRYLLLFPHHSFDL (SEQ ID NO: 2150)
I115C08	811	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHSFDL (SEQ ID NO: 2147)
I115C12	812	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHSFDT (SEQ ID NO: 2424)
I115D07	813	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYPLLF (SEQ ID NO: 2344)
I115E09	814	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHRFDL (SEQ ID NO: 2418)
I115F06	815	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRYLLLFPHYGMDV (SEQ ID NO: 2685)
I115F07	816	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRYLLLFPHYPLLF (SEQ ID NO: 2686)
I115F12	817	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRYLLLFPHHSFDL (SEQ ID NO: 2150)
I115G04	818	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHRFDL (SEQ ID NO: 2418)
I115G05	819	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYPLLF (SEQ ID NO: 2344)
I115G08	820	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHDSFDL (SEQ ID NO: 2631)
I115H04	821	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHANLSP (SEQ ID NO: 2503)

I115H07	822	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYPLLF (SEQ ID NO: 2344)
I115H09	823	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHRFDL (SEQ ID NO: 2418)
I116A07	824	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYEPLRF (SEQ ID NO: 2642)
I116B01	825	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHSFDL (SEQ ID NO: 2147)
I116B12	826	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHSFDL (SEQ ID NO: 2147)
I116C06	827	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYPLLF (SEQ ID NO: 2344)
I116D07	828	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHSFDL (SEQ ID NO: 2147)
I116E02	829	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHRFDL (SEQ ID NO: 2418)
I116E04	830	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHSFDL (SEQ ID NO: 2147)
I116F02	831	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRYLLLFPHHSFDL (SEQ ID NO: 2150)
I116F11	832	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYPLLF (SEQ ID NO: 2344)
I116G05	833	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQAPLSP (SEQ ID NO: 2699)
I001C09	834	143 - 250	164 - 174	190 - 196	229 - 239	1 - 127	26 - 35	50 - 66	99 - 116	DGSYDILTGYYIDNYMDV (SEQ ID NO: 2154)
I006D07	835	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	SHYDILTGLNYWYFDL (SEQ ID NO: 2166)
I007B03	836	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 66	99 - 116	DGSYDILTGYYIDNYMDV (SEQ ID NO: 2154)
I007F11	837	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 66	99 - 113	DGIDILLVPAALMDV (SEQ ID NO: 2160)
I007H08	838	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 37	52 - 69	102 - 117	DRYDILTGYYYYGMDV (SEQ ID NO: 2129)
I008A09	839	146 - 256	168 - 181	197 - 203	236 - 245	1 - 130	26 - 35	50 - 66	99 - 119	DREAYYDILTGYYLYYYYMDV (SEQ ID NO: 2172)
I008B01	840	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I008C02	841	145 - 255	167 - 180	196 - 202	235 - 244	1 - 129	26 - 37	52 - 67	100 - 118	HVRDYDILTGYYRGHYFDY (SEQ ID NO: 2167)
I008C03	842	143 - 250	164 - 174	190 - 196	229 - 239	1 - 127	26 - 35	50 - 65	98 - 116	EGSYDILTGYYVGVGRMDV (SEQ ID NO: 2171)
I008C12	843	146 - 256	168 - 181	197 - 203	236 - 245	1 - 130	26 - 35	50 - 68	101 - 119	FNPTYDILTGYYIGGYFQH (SEQ ID NO: 2155)
I012A06	844	145 - 254	169 - 179	195 - 201	234 - 243	1 - 129	26 - 37	52 - 67	100 - 118	GRWDYDLLTGEHLGYYFDY (SEQ ID NO: 2162)
I016E05	845	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I016F02	846	135 - 245	157 - 170	186 - 192	225 - 234	1 - 119	26 - 35	50 - 66	99 - 108	GMGDHYGMDV (SEQ ID NO: 2161)
I016F04	847	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I016H07	848	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	GYHDPLTSYNYNWFDP (SEQ ID NO: 2163)
I018C02	849	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I018C10	850	143 - 250	164 - 174	190 - 196	229 - 239	1 - 127	26 - 35	50 - 66	99 - 116	DGSYDILTGYYIDNYMDV (SEQ ID NO: 2154)
I018D07	851	143 - 250	164 - 174	190 - 196	229 - 239	1 - 127	26 - 35	50 - 66	99 - 116	DGSYDILTGYYIDNYMDV (SEQ ID NO: 2154)
I018H08	852	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I018H09	853	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I021B05	854	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGGNYDILTGYYIGNGAFDI (SEQ ID NO: 2158)
I022E02	855	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGLDI (SEQ ID NO: 2157)
I026E03	856	141 - 251	165 - 175	191 - 197	230 - 240	1 - 125	26 - 35	50 - 66	99 - 114	TDYDILTGYPMGYFDP (SEQ ID NO: 2173)

I027A07	857	144-- 255	167 - 179	195 - 201	234 - 244	1 - 128	26 - 35	50 - 66	99 - 117	GGEYDILTGYYFGLGVYDY (SEQ ID NO: 2170)
I028A06	858	142 - 253	164 - 176	192 - 198	231 - 242	1 - 126	26 - 35	50 - 66	99 - 115	GGDYDILTGLYYYGMDV (SEQ ID NO: 2156)
I029D07	859	141 - 250	163 - 176	192 - 198	231 - 239	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I029F11	860	143 - 253	165 - 177	193 - 199	232 - 242	1 - 127	26 - 35	50 - 66	99 - 116	DGSYDILTGYYIDNYMDV (SEQ ID NO: 2154)
I031C03	861	137 - 248	160 - 172	188 - 194	227 - 237	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
I031C07	862	147 - 258	170 - 183	199 - 205	238 - 247	1 - 131	26 - 35	50 - 66	99 - 120	SSPPRWYDALTGDSSYHSAMDV (SEQ ID NO: 2169)
I031F09	863	143 - 255	167 - 179	195 - 201	234 - 244	1 - 127	26 - 35	50 - 66	99 - 116	DEGRDLLTGYYWPNFFDS (SEQ ID NO: 2168)
I031G08	864	147 - 259	170 - 182	198 - 204	237 - 248	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWYDALTGHSSYHSAMDV (SEQ ID NO: 2159)
I031G10	865	147 - 258	170 - 182	198 - 204	237 - 247	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWYDALTGDSSYHSAMDV (SEQ ID NO: 2165)
I031G11	866	143 - 255	167 - 179	195 - 201	234 - 244	1 - 127	26 - 35	50 - 66	99 - 116	DEGRDLLTGYYWPNFFDS (SEQ ID NO: 2168)
I037E07	867	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 66	99 - 113	DGIDILLVPAALMDV (SEQ ID NO: 2160)
I037E12	868	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 66	99 - 113	DGIDILLVPAALMDV (SEQ ID NO: 2160)
I050A07	869	145 - 257	168 - 181	197 - 203	236 - 246	1 - 129	26 - 40	55 - 71	104 - 118	QDNDPLTGYKLGFDY (SEQ ID NO: 2164)
I061D02	870	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 37	52 - 69	102 - 117	DRYDILTGYYYYGMDV (SEQ ID NO: 2129)
I061E07	871	141 - 251	163 - 175	191 - 197	230 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I061H01	872	146 - 256	168 - 181	197 - 203	236 - 245	1 - 130	26 - 35	50 - 68	101 - 119	FNPTYDILTGYYIGGYFQH (SEQ ID NO: 2155)
I001A03	873	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	ERHYYDILTGYQTGYGMDV (SEQ ID NO: 2784)
I001A07	874	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I001A08	875	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I001A10	876	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I001A12	877	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I001B02	878	137 - 247	159 - 171	187 - 193	226 - 236	1 - 121	26 - 35	50 - 66	99 - 110	DRETKVGYGMDV (SEQ ID NO: 2945)
I001B07	879	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I001C06	880	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGGNYDILTGYYIGNGAFDI (SEQ ID NO: 2158)
I001C08	881	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	EGSYDILTGYYVGVGRMDV (SEQ ID NO: 2171)
I001C12	882	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I001D08	883	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 65	98 - 113	DSYDILTGYRGYYFDY (SEQ ID NO: 2745)
I001D12	884	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I001E05	885	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGGNYDILTGYYIGNGAFDI (SEQ ID NO: 2158)
I001E07	886	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I001G09	887	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I001H05	888	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	ERHYYDILTGYQTGYGMDV (SEQ ID NO: 2784)
I001H08	889	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I003A01	890	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
I003A06	891	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
I003A07	892	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYYDILTGYSYYGMDV (SEQ ID NO: 2135)

I003A10	893	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	MEYDILTGYYGGYFDY (SEQ ID NO: 2179)
I003B03	894	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
I003B04	895	138 - 248	162 - 172	188 - 194	227 - 237	1 - 122	25 - 34	49 - 65	98 - 111	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
I003B09	896	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYYDILTGYSYYGMDV (SEQ ID NO: 2135)
I003C01	897	140 - 252	164 - 176	192 - 198	231 - 241	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I003C02	898	141 - 252	164 - 176	192 - 198	231 - 241	1 - 125	26 - 35	50 - 66	99 - 114	GDYDILTGYPAECFQI (SEQ ID NO: 2854)
I003C03	899	141 - 250	164 - 174	190 - 196	229 - 239	1 - 125	26 - 35	50 - 66	99 - 114	GDYDILTGYPAECFQI (SEQ ID NO: 2854)
I003C12	900	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	MEYDILTGYYGGYFDY (SEQ ID NO: 2179)
I003D04	901	139 - 250	162 - 174	190 - 196	229 - 239	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
I003E05	902	141 - 253	164 - 176	192 - 198	231 - 242	1 - 125	26 - 35	50 - 66	99 - 114	GDYDILTGYPAECFQI (SEQ ID NO: 2854)
I003F01	903	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
I003F02	904	139 - 251	162 - 175	191 - 197	230 - 240	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
I003G01	905	143 - 254	168 - 179	195 - 201	234 - 243	1 - 127	26 - 35	50 - 66	99 - 116	GTGYDILTGYYMGSAFDQ (SEQ ID NO: 2800)
I003G05	906	143 - 255	166 - 179	195 - 201	234 - 244	1 - 127	26 - 35	50 - 66	99 - 116	GSGYDLLTGYFTGSPLDY (SEQ ID NO: 2766)
I003G06	907	145 - 256	168 - 181	197 - 203	236 - 245	1 - 129	26 - 35	50 - 66	99 - 118	DRGGNYDILTGYYFHHGVDV (SEQ ID NO: 2914)
I003G11	908	144 - 251	165 - 175	191 - 197	230 - 240	1 - 128	26 - 35	50 - 66	99 - 117	DAQSYYDILTGYQSYAFDI (SEQ ID NO: 2183)
I003H02	909	140 - 253	164 - 176	192 - 198	233 - 242	1 - 124	26 - 35	50 - 66	99 - 113	DNYDILTGYSRRFDP (SEQ ID NO: 2942)
I003H05	910	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
I003H08	911	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYYDILTGYSYYGMDV (SEQ ID NO: 2135)
I005A01	912	141 - 249	162 - 172	188 - 194	227 - 238	1 - 125	26 - 35	50 - 66	99 - 114	SHYDILTGLNYWYFDL (SEQ ID NO: 2166)
I005A02	913	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	EGRDILTGVYYYGLDV (SEQ ID NO: 2893)
I005B01	914	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	SHYDILTGLNYWYFDL (SEQ ID NO: 2166)
I005B09	915	137 - 247	159 - 172	188 - 194	227 - 236	1 - 121	26 - 35	50 - 65	98 - 110	TYYDILTGRFFDI (SEQ ID NO: 2866)
I005C01	916	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	SHYDILTGLNYWYFDL (SEQ ID NO: 2166)
I005D02	917	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	DLRYDILTGYHDAFDI (SEQ ID NO: 2890)
I005D03	918	142 - 249	165 - 175	191 - 197	230 - 238	1 - 126	26 - 35	50 - 66	99 - 115	GAYYDILTGYYPYGMDV (SEQ ID NO: 2860)
I005E01	919	142 - 249	165 - 175	191 - 197	230 - 238	1 - 126	26 - 35	50 - 66	99 - 115	GTYYDILTGYFHYGMDV (SEQ ID NO: 2774)
I005E08	920	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	SHYDILTGLNYWYFDL (SEQ ID NO: 2166)
I005F01	921	140 - 248	164 - 174	190 - 196	229 - 238	1 - 124	26 - 35	50 - 66	99 - 113	DQHDILTGVYYGMDV (SEQ ID NO: 2921)
I005F02	922	144 - 251	167 - 177	193 - 199	232 - 240	1 - 128	26 - 35	50 - 66	99 - 117	VSPSYDILTGYYLPHAFDV (SEQ ID NO: 2849)
I005F04	923	137 - 247	159 - 172	188 - 194	227 - 236	1 - 121	26 - 35	50 - 65	98 - 110	TYYDILTGRFFDI (SEQ ID NO: 2866)
I005F08	924	140 - 247	161 - 171	187 - 193	226 - 236	1 - 124	26 - 35	50 - 66	99 - 113	PSYDILTGYLYYFDY (SEQ ID NO: 2850)
I005G01	925	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	DLRYDILTGYHDAFDI (SEQ ID NO: 2890)
I005G08	926	142 - 249	165 - 175	191 - 197	230 - 238	1 - 126	26 - 35	50 - 66	99 - 115	GAYYDILTGYYPYGMDV (SEQ ID NO: 2860)
I005H02	927	140 - 247	161 - 171	187 - 193	226 - 236	1 - 124	26 - 35	50 - 66	99 - 113	GQYYDILTGYNWFDP (SEQ ID NO: 2857)
I006B01	928	139 - 246	160 - 170	186 - 192	225 - 235	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYGMDV (SEQ ID NO: 2133)

I006C09	929	143 - 253	165 - 177	193 - 199	232 - 242	1 - 127	26 - 35	50 - 66	99 - 116	GGYSSGWLRGGPYNWFDP (SEQ ID NO: 2967)
I006D09	930	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	GDYDILTGYYIPLRDY (SEQ ID NO: 2792)
I006E01	931	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 68	101 - 116	NLFDVWTLPYYYYMDV (SEQ ID NO: 2965)
I006E07	932	143 - 250	166 - 176	192 - 198	231 - 239	1 - 127	26 - 35	50 - 66	99 - 116	ADYDILTGYSPLTYGMDV (SEQ ID NO: 2762)
I006F01	933	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 68	101 - 113	MYYDILTGHNFDY (SEQ ID NO: 2879)
I006F02	934	142 - 253	164 - 176	192 - 198	231 - 242	1 - 126	26 - 35	50 - 66	99 - 115	VSRDILTGNYYYYGMDV (SEQ ID NO: 2817)
I006F07	935	143 - 253	165 - 177	193 - 199	232 - 242	1 - 127	26 - 35	50 - 66	99 - 116	GGYSSGWLRGGPYNWFDP (SEQ ID NO: 2967)
I006G01	936	146 - 253	169 - 179	195 - 201	234 - 242	1 - 130	26 - 35	50 - 68	101 - 119	AGGYYDILTGRDYYYGMDV (SEQ ID NO: 2877)
I006G04	937	132 - 239	153 - 163	179 - 185	218 - 228	1 - 116	26 - 35	50 - 66	99 - 105	RRYALDY (SEQ ID NO: 2920)
I006H01	938	146 - 253	167 - 177	193 - 199	232 - 242	1 - 130	26 - 35	50 - 65	98 - 119	DRGSYDILTGYYTPPHYYGMDV (SEQ ID NO: 2761)
I006H02	939	143 - 253	165 - 177	193 - 199	232 - 242	1 - 127	26 - 35	50 - 66	99 - 116	GGYSSGWLRGGPYNWFDP (SEQ ID NO: 2967)
I007A01	940	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I007A08	941	139 - 249	161 - 174	190 - 196	229 - 238	1 - 123	26 - 35	50 - 66	99 - 114	SHYDILTGLNYWYFDY (SEQ ID NO: 2746)
I007A11	942	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 66	99 - 113	ENYDFLTGYYGAFDI (SEQ ID NO: 2772)
I007A12	943	144 - 251	165 - 175	191 - 197	230 - 240	1 - 128	26 - 35	50 - 68	101 - 117	GIYDILTGYHWDGAFDI (SEQ ID NO: 2892)
I007B04	944	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I007C04	945	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I007C08	946	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 65	98 - 115	IRLYCYSLTGYYPYGMDD (SEQ ID NO: 2810)
I007C12	947	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 66	99 - 113	TNYDILTGYYQGVDY (SEQ ID NO: 2782)
I007D07	948	140 - 247	161 - 171	187 - 193	226 - 236	1 - 124	26 - 35	50 - 66	99 - 113	GQYYDILTGYNWFDP (SEQ ID NO: 2857)
I007D08	949	144 - 251	165 - 175	191 - 197	230 - 240	1 - 128	26 - 35	50 - 68	101 - 117	GIYDILTGYHWDDAFDI (SEQ ID NO: 2872)
I007E03	950	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I007E10	951	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	DFYDILTGYPLGGMDV (SEQ ID NO: 2741)
I007E11	952	144 - 251	165 - 175	191 - 197	230 - 240	1 - 128	26 - 35	50 - 66	99 - 117	DLPYYDILTGYSLTSGMDV (SEQ ID NO: 2923)
I007F06	953	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I007F08	954	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 65	98 - 116	GRRYDILTGYYYYHHGMDV (SEQ ID NO: 2811)
I007G07	955	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	SHYDILTGLNYWYFDL (SEQ ID NO: 2166)
I007G09	956	142 - 252	164 - 177	193 - 199	232 - 241	1 - 126	26 - 35	50 - 66	99 - 115	DSGGDILTGYYMPYFDY (SEQ ID NO: 2847)
I007G10	957	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 65	98 - 115	VGLYYDILTGYYPSGMDV (SEQ ID NO: 2805)
I007H07	958	147 - 257	169 - 182	198 - 204	237 - 246	1 - 131	26 - 35	50 - 68	101 - 120	SQAHYDILTGYYLWSYGMDV (SEQ ID NO: 2875)
I007H11	959	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ESYDILTGYRHYGMDL (SEQ ID NO: 2891)
I008A02	960	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I008A05	961	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I008A06	962	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I008A07	963	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DREYDLLTGYYLHAFDM (SEQ ID NO: 2960)
I008A12	964	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 66	99 - 113	ENYDFLTGYYGAFDI (SEQ ID NO: 2772)

I008B02	965	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I008B04	966	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 66	99 - 116	DGSYDILTGYYIDNYMDV (SEQ ID NO: 2154)
I008B05	967	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	DHYDILTGLYYYGMDV (SEQ ID NO: 2760)
I008B06	968	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I008B07	969	140 - 247	163 - 173	189 - 195	228 - 236	1 - 124	24 - 33	48 - 64	97 - 113	GRRYDILTGYYKGPLDY (SEQ ID NO: 2902)
I008B10	970	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	AYYDNLTGFLPYGMGV (SEQ ID NO: 2947)
I008B11	971	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	EGYDILTGYFLDYYHGMDV (SEQ ID NO: 2753)
I008C06	972	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I008C08	973	149 - 259	171 - 183	199 - 205	238 - 248	1 - 133	26 - 35	50 - 66	99 - 122	GPRGGPYYDILTGYYLSLSDAFDI (SEQ ID NO: 2729)
I008C09	974	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	EYYDILTGYRDPYGMDV (SEQ ID NO: 2973)
I008D01	975	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I008D02	976	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I008D03	977	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	EVRNYDLLTRSYLAGPLDN (SEQ ID NO: 2751)
I008D04	978	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I008D05	979	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I008D06	980	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I008D07	981	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	DRGYYDILTGYYRGHGMDV (SEQ ID NO: 2837)
I008D08	982	144 - 251	165 - 175	191 - 197	230 - 240	1 - 128	26 - 35	50 - 66	99 - 117	DLPYYDILTGYSLTSGMDV (SEQ ID NO: 2923)
I008D12	983	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	EEGFYDILTGYYGPGYFDY (SEQ ID NO: 2974)
I008E01	984	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I008E02	985	137 - 247	159 - 172	188 - 194	227 - 236	1 - 121	20 - 31	46 - 63	96 - 110	EGYDILTGYSKFLDY (SEQ ID NO: 2906)
I008E03	986	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I008E04	987	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I008E08	988	141 - 252	163 - 175	191 - 197	230 - 241	1 - 125	26 - 35	50 - 66	99 - 114	SHYDILTGLNYWYFDL (SEQ ID NO: 2166)
I008E09	989	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 66	99 - 116	ERADYDILTGYYFYDMDV (SEQ ID NO: 2833)
I008E12	990	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 37	52 - 67	100 - 114	FRYDILTSYYYGMDV (SEQ ID NO: 2734)
I008F03	991	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I008F06	992	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I008F07	993	143 - 250	164 - 174	190 - 196	229 - 239	1 - 127	26 - 35	50 - 65	98 - 116	GRRYDILTGYYYYHHGMDV (SEQ ID NO: 2811)
I008F08	994	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 66	99 - 116	GHYDILTGYDDYYYGMDV (SEQ ID NO: 2844)
I008F09	995	133 - 243	155 - 168	184 - 190	223 - 232	1 - 117	26 - 35	50 - 65	98 - 106	HDILTGFDY (SEQ ID NO: 2904)
I008F10	996	140 - 247	161 - 171	187 - 193	226 - 236	1 - 124	26 - 35	50 - 66	99 - 113	SGYDILTGYLYGMDV (SEQ ID NO: 2934)
I008F11	997	144 - 251	165 - 175	191 - 197	230 - 240	1 - 128	26 - 35	50 - 68	101 - 117	APYDILTGYSDYYGMDV (SEQ ID NO: 2968)
I008G02	998	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I008G03	999	140 - 247	161 - 171	187 - 193	226 - 236	1 - 124	26 - 35	50 - 66	99 - 113	GDYDPLTGYSFGVDV (SEQ ID NO: 2941)

I008G04	1000	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 65	98 - 116	EGSYDILTGYYVGVGRMDV (SEQ ID NO: 2171)
I008G05	1001	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	DGYYDILTGGFYYYYGMDV (SEQ ID NO: 2899)
I008G11	1002	136 - 246	158 - 171	187 - 193	226 - 235	1 - 120	26 - 35	50 - 66	99 - 109	AYYDILTGLDY (SEQ ID NO: 2966)
I008G12	1003	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 66	99 - 116	DQQYDILTGYYIHYGMDV (SEQ ID NO: 2964)
I008H02	1004	141 - 248	164 - 174	190 - 196	229 - 237	1 - 125	26 - 35	50 - 66	99 - 114	DQVDLLLMDHNYYMDV (SEQ ID NO: 2918)
I008H03	1005	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I008H06	1006	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 65	98 - 116	EGSYDILTGYYVGVGRMDV (SEQ ID NO: 2171)
I008H09	1007	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 66	99 - 116	DQQYDILTGYYIHYGMDV (SEQ ID NO: 2964)
I008H11	1008	141 - 248	164 - 174	190 - 196	229 - 237	1 - 125	26 - 35	50 - 66	99 - 114	TKYDILTGYYYYYMDV (SEQ ID NO: 2856)
I012B03	1009	140 - 249	163 - 175	191 - 197	230 - 238	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I012B06	1010	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I012B10	1011	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I012C03	1012	142 - 255	165 - 178	194 - 200	233 - 244	1 - 126	26 - 35	50 - 66	99 - 115	TDRFGAKDVTSRWGMDV (SEQ ID NO: 2814)
I012C06	1013	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I012C09	1014	140 - 250	164 - 174	190 - 196	229 - 239	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I012D12	1015	145 - 256	168 - 180	196 - 202	235 - 245	1 - 129	26 - 35	50 - 66	99 - 118	DRGGNYDILTGYYFHHGVDV (SEQ ID NO: 2914)
I012E07	1016	140 - 252	164 - 176	192 - 198	231 - 241	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I012E08	1017	139 - 250	162 - 174	190 - 196	229 - 239	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
I012E09	1018	140 - 247	163 - 173	189 - 195	228 - 236	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I012F05	1019	140 - 249	163 - 173	189 - 195	228 - 238	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I012F12	1020	140 - 251	164 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I012G03	1021	140 - 252	164 - 176	192 - 198	231 - 241	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I012G05	1022	139 - 250	163 - 173	189 - 195	228 - 239	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
I012G10	1023	139 - 251	162 - 175	191 - 197	230 - 240	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
I012H09	1024	140 - 249	163 - 173	189 - 195	228 - 238	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I013A10	1025	147 - 259	170 - 182	198 - 204	237 - 248	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWYDALTGHSSYHSAMDV (SEQ ID NO: 2159)
I013A12	1026	147 - 256	171 - 181	197 - 203	236 - 245	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWYDALTGHSSYHSAMDV (SEQ ID NO: 2159)
I013B04	1027	147 - 256	172 - 182	198 - 204	237 - 245	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWYDALTGDSSYHSAMDV (SEQ ID NO: 2165)
I013B09	1028	147 - 257	171 - 181	197 - 203	236 - 246	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWYDALTGHSSYHSAMDV (SEQ ID NO: 2159)
I013C02	1029	147 - 258	170 - 182	198 - 204	237 - 247	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWYDALTGDSSYRSAMDV (SEQ ID NO: 2818)
I013C04	1030	137 - 249	161 - 173	189 - 195	228 - 238	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
I013D02	1031	137 - 248	160 - 173	189 - 195	228 - 237	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
I013D03	1032	147 - 259	170 - 183	199 - 205	238 - 248	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWYDALTGDSSYHSAMDV (SEQ ID NO: 2165)
I013D10	1033	145 - 257	168 - 181	197 - 203	236 - 246	1 - 129	26 - 35	50 - 66	99 - 118	GLRHVTLFGTGTRGHFYMDV (SEQ ID NO: 2789)
I013E02	1034	147 - 259	170 - 183	199 - 205	238 - 248	1 - 131	26 - 35	50 - 66	99 - 120	GREDTDKVKPWDRYYHYYYMDV (SEQ ID NO: 2809)

I013E05	1035	137 - 249	162 - 173	189 - 195	228 - 238	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
I013E09	1036	147 - 260	170 - 183	199 - 205	238 - 249	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWYDALTGDSSYHSAMDV (SEQ ID NO: 2165)
I013F03	1037	137 - 248	160 - 172	188 - 194	227 - 237	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
I013F04	1038	147 - 258	170 - 182	198 - 204	237 - 247	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWYDALTGHSSYHSAMDV (SEQ ID NO: 2159)
I013F07	1039	145 - 260	170 - 185	201 - 207	240 - 249	1 - 129	26 - 35	50 - 66	99 - 118	AATTSQKHNKYAYYFYGMDV (SEQ ID NO: 2131)
I013F09	1040	137 - 248	160 - 172	188 - 194	227 - 237	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
I013F10	1041	147 - 259	170 - 183	199 - 205	238 - 248	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWYDALTGHSSYHSAMDV (SEQ ID NO: 2159)
I013H04	1042	147 - 258	170 - 182	198 - 204	237 - 247	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWYDALTGHSSYHSAMDV (SEQ ID NO: 2159)
I013H07	1043	147 - 259	170 - 183	199 - 205	238 - 248	1 - 131	26 - 35	50 - 66	99 - 120	GREDTDKVKPWDRYYHYYYMDV (SEQ ID NO: 2809)
I014A12	1044	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGGNYDILTGYYIGNGAFDI (SEQ ID NO: 2158)
I014C06	1045	141 - 254	164 - 177	193 - 200	233 - 243	1 - 125	26 - 35	50 - 66	99 - 114	GDYDILTGYPAECFQI (SEQ ID NO: 2854)
I014C10	1046	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I014C12	1047	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I014E06	1048	140 - 252	164 - 176	192 - 198	231 - 241	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I014F02	1049	141 - 251	166 - 176	192 - 198	231 - 240	1 - 125	26 - 37	52 - 67	100 - 114	AGYDLLTGYPFYFDS (SEQ ID NO: 2757)
I016A08	1050	144 - 251	165 - 175	191 - 197	230 - 240	1 - 128	26 - 35	50 - 66	99 - 117	EVRNYDLLTRSYLAGPLDN (SEQ ID NO: 2751)
I016A09	1051	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I016C02	1052	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I016C03	1053	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I016C05	1054	148 - 255	169 - 179	195 - 201	234 - 244	1 - 132	26 - 35	50 - 66	99 - 121	VQMDSEYYDLLTGINVGPYYFDY (SEQ ID NO: 2132)
I016C09	1055	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I016C11	1056	148 - 255	169 - 179	195 - 201	234 - 244	1 - 132	26 - 35	50 - 66	99 - 121	VQMDSEYYDLLTGINVGPYYFDY (SEQ ID NO: 2132)
I016D10	1057	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I016D11	1058	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I016E03	1059	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I016E04	1060	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I016F03	1061	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I016F11	1062	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I016G01	1063	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I016G06	1064	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I016G12	1065	148 - 255	169 - 179	195 - 201	234 - 244	1 - 132	26 - 35	50 - 66	99 - 121	VQMDSEYYDLLTGINVGPYYFDY (SEQ ID NO: 2132)
I016H10	1066	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)

I017A06	1067	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I017A07	1068	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I017A11	1069	140 - 253	162 - 175	191 - 197	233 - 242	1 - 124	25 - 34	49 - 65	98 - 113	ATYDPLTGYSFDGLDI (SEQ ID NO: 2157)
I017E12	1070	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I017G03	1071	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I017G07	1072	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I017H01	1073	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I018A02	1074	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I018A04	1075	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	EGSYDILTGYYVGVGRMDV (SEQ ID NO: 2171)
I018A05	1076	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I018A11	1077	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I018B02	1078	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I018B08	1079	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I018C04	1080	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I018D02	1081	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I018E06	1082	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I018E08	1083	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I018F04	1084	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I018G06	1085	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I018H07	1086	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I019E05	1087	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	ERHYYDILTGYQTGYGMDV (SEQ ID NO: 2784)
I019F06	1088	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	ERHYYDILTGYQTGYGMDV (SEQ ID NO: 2784)
I019G12	1089	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGGNYDILTGYYIGNGAFDI (SEQ ID NO: 2158)
I020D01	1090	137 - 247	159 - 171	187 - 193	226 - 236	1 - 121	26 - 35	50 - 66	99 - 110	DRETKVGYGMDV (SEQ ID NO: 2945)
I020D05	1091	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGGNYDILTGYYIGNGAFDI (SEQ ID NO: 2158)
I020E10	1092	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGGNYDILTGYYIGNGAFDI (SEQ ID NO: 2158)
I020G12	1093	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGGNYDILTGYYIGNGAFDI (SEQ ID NO: 2158)
I020H06	1094	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGGNYHILTGYYIGNGAFDI (SEQ ID NO: 2896)
I020H10	1095	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGENYDILTGYYIGNGAFDI (SEQ ID NO: 2903)
I021A11	1096	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGGNYDILTGYYIGNGAFDI (SEQ ID NO: 2158)
I021B01	1097	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGGNYDILTGYYIGNGAFDI (SEQ ID NO: 2158)
I021C11	1098	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGGNYDILTGYYIGNGAFDI (SEQ ID NO: 2158)
I021D12	1099	137 - 247	159 - 171	187 - 193	226 - 236	1 - 121	26 - 35	50 - 66	99 - 110	DRETKVGYGMDV (SEQ ID NO: 2945)
I021E10	1100	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGGNYDILTGYYIGNGAFDI (SEQ ID NO: 2158)
I021G02	1101	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGGNYDILTGYYIGNGAFDI (SEQ ID NO: 2158)
I022A08	1102	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYYDILTGYSYYGMDV (SEQ ID NO: 2135)

I022B01	1103	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I022B10	1104	141 - 248	164 - 174	190 - 196	229 - 237	1 - 125	26 - 35	50 - 66	99 - 114	MEYDILTGYYGGYFDY (SEQ ID NO: 2179)
I022C02	1105	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYYDILTGYSYYGMDV (SEQ ID NO: 2135)
I022C04	1106	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I022C08	1107	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I022D06	1108	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYYDILTGYSYYGMDV (SEQ ID NO: 2135)
I022E08	1109	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	ASYYDILTGYYKGAFDI (SEQ ID NO: 2855)
I022F01	1110	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYYDILTGYSYYGMDV (SEQ ID NO: 2135)
I022F04	1111	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYYDILTGYSYYGMDV (SEQ ID NO: 2135)
I022F12	1112	140 - 247	161 - 171	187 - 193	226 - 236	1 - 124	26 - 35	50 - 66	99 - 113	GDYDILTGTYYYIDV (SEQ ID NO: 2859)
I022G11	1113	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYYDILTGYSYYGMDV (SEQ ID NO: 2135)
I023D01	1114	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	SHYDILTGLNYWYFDL (SEQ ID NO: 2166)
I023D04	1115	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYYDILTGYSYYGMDV (SEQ ID NO: 2135)
I024B04	1116	140 - 247	161 - 171	187 - 193	226 - 236	1 - 124	26 - 35	50 - 66	99 - 113	VYYDILTGYNLFFDY (SEQ ID NO: 2177)
I024D01	1117	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYYDILTGYSYYGMDV (SEQ ID NO: 2135)
I024F06	1118	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYYDILTGYSYYGMDV (SEQ ID NO: 2135)
I024H01	1119	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYYDILTGYSYYGMDV (SEQ ID NO: 2135)
I024H07	1120	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYYDILTGYSYYGMDV (SEQ ID NO: 2135)
I025A01	1121	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
I025A04	1122	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I025A07	1123	140 - 249	163 - 173	189 - 195	228 - 238	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I025B01	1124	133 - 244	156 - 168	184 - 190	223 - 233	1 - 117	26 - 35	50 - 66	99 - 106	DQGRYLDL (SEQ ID NO: 2175)
I025B10	1125	140 - 253	164 - 176	192 - 198	233 - 242	1 - 124	26 - 35	50 - 66	99 - 113	DNYDILTGYSRRFDP (SEQ ID NO: 2942)
I025B12	1126	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
I025C07	1127	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
I025D11	1128	140 - 252	164 - 176	192 - 198	231 - 241	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I025E04	1129	142 - 252	164 - 176	192 - 198	231 - 241	1 - 126	26 - 35	50 - 66	99 - 115	PLGITAVRGAKTDAFGI (SEQ ID NO: 2929)
I025E05	1130	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I025E07	1131	140 - 252	164 - 176	192 - 198	231 - 241	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I025E10	1132	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I025F01	1133	139 - 251	162 - 175	191 - 197	230 - 240	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
I025F08	1134	137 - 248	160 - 172	188 - 194	227 - 237	1 - 121	26 - 35	50 - 66	99 - 110	GGSSQNFYGMDV (SEQ ID NO: 2884)
I025G03	1135	140 - 252	164 - 176	192 - 198	231 - 241	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I025G08	1136	140 - 254	163 - 176	192 - 198	231 - 243	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I025H02	1137	144 - 255	167 - 179	195 - 201	234 - 244	1 - 128	26 - 35	50 - 65	98 - 117	AGSGFHDILTGYYKGGYFDY (SEQ ID NO: 2961)
I026A01	1138	141 - 249	165 - 175	191 - 197	230 - 238	1 - 125	26 - 35	50 - 66	99 - 114	GDYDILTGYPAECFQI (SEQ ID NO: 2854)

I026B01	1139	143 - 254	166 - 178	194 - 200	233 - 243	1 - 127	26 - 35	50 - 66	99 - 116	GSVYDILTGTYYKSGMGV (SEQ ID NO: 2733)
I026B06	1140	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
I026C06	1141	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
I026C10	1142	138 - 249	161 - 174	190 - 196	229 - 238	1 - 122	26 - 34	49 - 65	98 - 111	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
I026C11	1143	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I026D09	1144	139 - 252	162 - 175	191 - 197	230 - 241	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
I026E04	1145	140 - 252	164 - 176	192 - 198	231 - 241	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I026E06	1146	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 35	50 - 66	99 - 113	GYDDILTGYIMALDY (SEQ ID NO: 2821)
I026E09	1147	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
I026F01	1148	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
I026F09	1149	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
I026F12	1150	140 - 256	163 - 176	192 - 202	237 - 245	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
I026G08	1151	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
I026G10	1152	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
I026G11	1153	143 - 255	166 - 179	195 - 201	234 - 244	1 - 127	26 - 35	50 - 66	99 - 116	GTGYDILTGYYMGSAFDQ (SEQ ID NO: 2800)
I026H02	1154	139 - 251	162 - 175	191 - 197	230 - 240	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
I026H06	1155	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I026H10	1156	144 - 255	167 - 179	195 - 201	234 - 244	1 - 128	26 - 35	50 - 66	99 - 117	GGEYDILTGYYFGLGVYDY (SEQ ID NO: 2170)
I027A09	1157	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
I027B02	1158	139 - 250	162 - 174	190 - 196	229 - 239	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
I027B05	1159	140 - 250	163 - 176	192 - 198	230 - 239	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
I027C08	1160	138 - 249	161 - 174	190 - 196	229 - 238	1 - 122	26 - 34	49 - 63	96 - 111	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
I027D02	1161	141 - 250	164 - 174	190 - 196	229 - 239	1 - 125	26 - 35	50 - 66	99 - 114	DPFGAVPGYYYYAMDV (SEQ ID NO: 2826)
I027E03	1162	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
I027E05	1163	140 - 252	164 - 176	192 - 198	231 - 241	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I027F04	1164	144 - 252	167 - 176	192 - 198	231 - 241	1 - 128	26 - 35	50 - 66	99 - 117	GPWYDPLFPPSGRHYGLDV (SEQ ID NO: 2793)
I027F05	1165	140 - 254	163 - 176	192 - 198	231 - 243	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I027F11	1166	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
I027G06	1167	140 - 253	164 - 176	192 - 198	233 - 242	1 - 124	26 - 35	50 - 66	99 - 113	DNYDILTGYSRRFDP (SEQ ID NO: 2942)
I027G07	1168	140 - 250	164 - 174	190 - 196	229 - 239	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I027H03	1169	141 - 252	164 - 176	192 - 198	231 - 241	1 - 125	26 - 35	50 - 66	99 - 114	GDYDILTGYPAECFQI (SEQ ID NO: 2854)
I028A04	1170	143 - 250	164 - 174	190 - 196	229 - 239	1 - 127	26 - 35	50 - 66	99 - 116	DMYYDILTGYYTGLAFDM (SEQ ID NO: 2880)
I028A07	1171	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	VLNYDILTGYYYGMDV (SEQ ID NO: 2832)
I028B08	1172	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I028B10	1173	148 - 258	170 - 183	199 - 205	238 - 247	1 - 132	26 - 35	50 - 68	101 - 121	DFGYYDILTGYYIGAFYAFDI (SEQ ID NO: 2861)
I028C01	1174	142 - 250	165 - 175	191 - 197	230 - 239	1 - 126	26 - 37	52 - 69	102 - 115	GGHTCIIPTCHMGG (SEQ ID NO: 2796)

I028C04	1175	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 66	99 - 116	DMYYDILTGYYTGLAFDM (SEQ ID NO: 2880)
I028C08	1176	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I028D04	1177	140 - 247	163 - 173	189 - 195	228 - 236	1 - 124	26 - 35	50 - 65	98 - 113	ATQDILTGYLYSGMDV (SEQ ID NO: 2977)
I028D05	1178	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	EHYDILTGYSLLGMDV (SEQ ID NO: 2907)
I028D12	1179	143 - 250	164 - 174	190 - 196	229 - 239	1 - 127	26 - 35	50 - 66	99 - 116	DGYYDILTGYSVYYGMDV (SEQ ID NO: 2938)
I028E06	1180	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 65	98 - 116	EGSYDILTGYYVGVGRMDV (SEQ ID NO: 2171)
I028E07	1181	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I028E08	1182	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I028F06	1183	146 - 256	168 - 180	196 - 202	235 - 245	1 - 130	26 - 35	50 - 66	99 - 119	DDRRGYYDILTGYYRFGSFDI (SEQ ID NO: 2901)
I028F08	1184	134 - 244	156 - 169	185 - 191	224 - 233	1 - 118	26 - 35	50 - 66	99 - 107	DIDIGGDDS (SEQ ID NO: 2954)
I028G08	1185	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	VSGYNSGYFESYDMDV (SEQ ID NO: 2732)
I028G09	1186	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	EVRNYDLLTRSYLAGPLDN (SEQ ID NO: 2751)
I028G10	1187	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I028H02	1188	142 - 249	165 - 175	191 - 197	230 - 238	1 - 126	26 - 37	52 - 69	102 - 115	SGEPCITLACNLGG (SEQ ID NO: 2797)
I028H03	1189	148 - 256	169 - 179	195 - 201	234 - 245	1 - 132	26 - 35	50 - 66	99 - 121	DASEYYDILTGYYLATGRNWFDP (SEQ ID NO: 2888)
I028H06	1190	145 - 255	167 - 180	196 - 202	235 - 244	1 - 129	26 - 35	50 - 66	99 - 118	DPSPYYDILTGYFLPYYMDV (SEQ ID NO: 2843)
I028H09	1191	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 68	101 - 113	EIDDILTGYYMDV (SEQ ID NO: 2905)
I029A10	1192	139 - 246	160 - 170	186 - 192	225 - 235	1 - 123	26 - 35	50 - 65	98 - 112	MNYDILTGLVNWFDP (SEQ ID NO: 2786)
I029A12	1193	137 - 247	159 - 171	187 - 193	226 - 236	1 - 121	26 - 35	50 - 68	101 - 110	RDILTGFYDS (SEQ ID NO: 2933)
I029B11	1194	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I029C08	1195	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	EGSYDILTGYYVGVGRMDV (SEQ ID NO: 2171)
I029E10	1196	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	EVRNYDLLTRSYLAGPLDN (SEQ ID NO: 2751)
I029F08	1197	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	EVRNYDLLTRSYLAGPLDN (SEQ ID NO: 2751)
I029G08	1198	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	GYYDILTGYQSDAFDI (SEQ ID NO: 2927)
I030A02	1199	142 - 253	165 - 177	193 - 199	232 - 242	1 - 126	26 - 35	50 - 66	99 - 115	TERFGAKDVTARWGMDV (SEQ ID NO: 2874)
I030A03	1200	140 - 253	163 - 175	191 - 197	230 - 242	1 - 124	26 - 35	50 - 66	99 - 113	ENYDILTGYYNFFDY (SEQ ID NO: 2737)
I030A04	1201	140 - 252	163 - 176	192 - 198	231 - 241	1 - 124	26 - 35	50 - 66	99 - 113	RQYDILTGYYGGFDY (SEQ ID NO: 2958)
I030A05	1202	140 - 249	163 - 175	191 - 197	230 - 238	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I030A09	1203	139 - 250	162 - 174	190 - 196	229 - 239	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
I030A12	1204	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
I030B06	1205	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
I030B08	1206	140 - 247	163 - 173	189 - 195	228 - 236	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I030B10	1207	141 - 251	165 - 175	191 - 197	230 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ELGHREGGYWYSPYNV (SEQ ID NO: 2838)
I030C03	1208	139 - 252	162 - 175	191 - 197	230 - 241	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
I030C06	1209	146 - 256	169 - 182	198 - 204	237 - 245	1 - 130	26 - 35	50 - 68	101 - 119	DPGNYDILTGYYYYYGMDV (SEQ ID NO: 2935)

I030C08	1210	133 - 244	156 - 168	184 - 190	223 - 233	1 - 117	26 - 35	50 - 66	99 - 106	SGPGWFDP (SEQ ID NO: 2870)
I030C09	1211	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I030C10	1212	140 - 250	163 - 175	191 - 197	230 - 239	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I030C11	1213	139 - 251	162 - 175	191 - 197	230 - 240	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
I030C12	1214	133 - 244	156 - 168	184 - 190	223 - 233	1 - 117	26 - 35	50 - 66	99 - 106	SGPGWFDP (SEQ ID NO: 2870)
I030D07	1215	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
I030D12	1216	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I030E02	1217	139 - 251	162 - 175	191 - 197	230 - 240	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
I030E05	1218	140 - 252	164 - 176	192 - 198	231 - 241	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I030E07	1219	140 - 251	165 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I030E08	1220	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I030E09	1221	140 - 252	163 - 176	192 - 198	231 - 241	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I030E10	1222	139 - 250	162 - 174	190 - 196	229 - 239	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
I030F02	1223	141 - 252	164 - 176	192 - 198	231 - 241	1 - 125	26 - 37	52 - 67	100 - 114	AGYDLLTGYPFYFDS (SEQ ID NO: 2757)
I030F05	1224	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I030F06	1225	139 - 251	162 - 175	191 - 197	230 - 240	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
I030F08	1226	140 - 254	163 - 176	192 - 198	231 - 243	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I030F09	1227	140 - 253	164 - 176	192 - 198	231 - 242	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I030F11	1228	139 - 250	162 - 174	190 - 196	229 - 239	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
I030F12	1229	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 35	50 - 66	99 - 113	DNYDILTGYSRRFDP (SEQ ID NO: 2942)
I030G03	1230	140 - 256	163 - 176	192 - 202	237 - 245	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I030G07	1231	139 - 251	162 - 175	191 - 197	230 - 240	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
I030G09	1232	140 - 251	164 - 174	190 - 196	229 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I030H05	1233	145 - 255	168 - 181	197 - 203	236 - 244	1 - 129	26 - 35	50 - 66	99 - 118	DRGGNYDILTGYYFHHGVDV (SEQ ID NO: 2914)
I030H06	1234	146 - 258	170 - 182	198 - 204	239 - 247	1 - 130	26 - 37	52 - 69	102 - 119	ATKSYDILTRMYYYHMDV (SEQ ID NO: 2748)
I030H10	1235	140 - 253	163 - 176	192 - 198	231 - 242	1 - 124	26 - 35	50 - 66	99 - 113	DNYDILTGYSRRFDP (SEQ ID NO: 2942)
I030H11	1236	140 - 252	164 - 176	192 - 198	231 - 241	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
I031A01	1237	137 - 248	160 - 173	189 - 195	228 - 237	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
I031A03	1238	141 - 251	166 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PYYDPLTAYTFQYFGN (SEQ ID NO: 2806)
I031A08	1239	147 - 258	170 - 182	198 - 204	237 - 247	1 - 131	26 - 35	50 - 66	99 - 120	GREDTDKVKPWDRYYHYYYMDV (SEQ ID NO: 2809)
I031A12	1240	146 - 257	169 - 181	197 - 203	236 - 246	1 - 130	26 - 35	50 - 66	99 - 119	GREDTDKVKPWDRYYHYYMDV (SEQ ID NO: 2972)
I031B03	1241	136 - 246	159 - 172	188 - 194	227 - 235	1 - 120	26 - 35	50 - 68	101 - 109	GLGHTDSDS (SEQ ID NO: 2959)
I031B06	1242	142 - 253	165 - 177	193 - 199	232 - 242	1 - 126	26 - 35	50 - 66	99 - 115	AKGYYYDSSGASDVFDV (SEQ ID NO: 2871)
I031B07	1243	147 - 258	170 - 182	198 - 204	237 - 247	1 - 131	26 - 35	50 - 66	99 - 120	GREDTDKVKPWDRYYHYYYMDV (SEQ ID NO: 2809)

I031B08	1244	147 - 260	171 - 183	199 - 205	238 - 249	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWYDALTGHSSYHSAMDV (SEQ ID NO: 2159)
I031B09	1245	147 - 258	170 - 182	198 - 204	237 - 247	1 - 131	26 - 35	50 - 66	99 - 120	SNPPKWYDALTGHSSYHSAMDV (SEQ ID NO: 2840)
I031B11	1246	137 - 248	160 - 172	188 - 194	227 - 237	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
I031B12	1247	147 - 259	170 - 183	199 - 205	238 - 248	1 - 131	26 - 35	50 - 66	99 - 120	GREDTDKVKPWDRYYHYYYMDV (SEQ ID NO: 2809)
I031C01	1248	137 - 248	160 - 172	188 - 194	227 - 237	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
I031C02	1249	141 - 253	164 - 177	193 - 199	232 - 242	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
I031C04	1250	147 - 260	171 - 183	199 - 205	238 - 249	1 - 131	26 - 35	50 - 66	99 - 120	GRKDTDKVKPWDRYYHYYYMDV (SEQ ID NO: 2813)
I031C08	1251	137 - 248	161 - 171	187 - 193	226 - 237	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
I031C11	1252	147 - 257	171 - 181	197 - 203	236 - 246	1 - 131	26 - 35	50 - 66	99 - 120	GREDTDKVKPWDRYYHYYYMDV (SEQ ID NO: 2809)
I031D01	1253	145 - 256	168 - 180	196 - 202	235 - 245	1 - 129	26 - 35	50 - 66	99 - 118	AATTSQKHNKYAYYFYGMDV (SEQ ID NO: 2131)
I031D04	1254	137 - 248	160 - 172	188 - 194	227 - 237	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
I031D06	1255	147 - 258	170 - 182	198 - 204	237 - 247	1 - 131	26 - 35	50 - 66	99 - 120	GREDTDKVKLWDRYYHYYYMDV (SEQ ID NO: 2807)
I031D08	1256	144 - 257	167 - 180	196 - 202	235 - 246	1 - 128	26 - 35	50 - 66	99 - 117	VRPKLRYFDWLSRHDAFDL (SEQ ID NO: 2820)
I031D09	1257	137 - 247	161 - 171	187 - 193	226 - 236	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
I031D11	1258	147 - 256	171 - 181	197 - 203	236 - 245	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWYDALTGDSSYHSAMDV (SEQ ID NO: 2165)
I031D12	1259	144 - 254	168 - 178	194 - 200	233 - 243	1 - 128	26 - 35	50 - 66	99 - 117	DKAHGEYGRDYYYYYGMDV (SEQ ID NO: 2735)
I031E01	1260	147 - 258	170 - 182	198 - 204	237 - 247	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWYDALTGHSSYHSAMDV (SEQ ID NO: 2159)
I031E05	1261	147 - 257	171 - 181	197 - 203	236 - 246	1 - 131	26 - 35	50 - 66	99 - 120	SGPPKWYDALTGHSSYHSAMDV (SEQ ID NO: 2848)
I031E07	1262	147 - 259	170 - 182	198 - 204	237 - 248	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWYDALTGHSSYHSAMDV (SEQ ID NO: 2159)
I031E08	1263	147 - 259	170 - 183	199 - 205	238 - 248	1 - 131	26 - 35	50 - 66	99 - 120	GREDTDKVKPWDRYYHYYYMDV (SEQ ID NO: 2809)
I031E09	1264	137 - 246	162 - 173	189 - 195	228 - 235	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
I031E10	1265	147 - 258	170 - 182	198 - 204	237 - 247	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWYDALTGDSSYHSAMDV (SEQ ID NO: 2165)
I031E11	1266	147 - 258	170 - 182	198 - 204	237 - 247	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWYDALTGHSSYHSAMDV (SEQ ID NO: 2159)
I031F01	1267	137 - 248	160 - 172	188 - 194	227 - 237	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
I031F04	1268	137 - 246	162 - 172	188 - 194	227 - 235	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
I031F06	1269	135 - 247	159 - 171	187 - 193	226 - 236	1 - 119	26 - 35	50 - 66	99 - 108	DTVRSGGMDV (SEQ ID NO: 2804)
I031F10	1270	147 - 259	170 - 183	199 - 205	238 - 248	1 - 131	26 - 35	50 - 66	99 - 120	GREDTDKVKPWDRYYHYYYMDV (SEQ ID NO: 2809)
I031F11	1271	144 - 255	167 - 179	195 - 201	234 - 244	1 - 128	26 - 35	50 - 66	99 - 117	DKAHGEYGRDYYYYYGMDV (SEQ ID NO: 2735)
I031F12	1272	137 - 249	160 - 172	188 - 194	227 - 238	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
I031G01	1273	137 - 248	160 - 172	188 - 194	227 - 237	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)

I031G03	1274	147 - 258	170 - 182	198 - 204	237 - 247	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWYDALTGHSSYHSAMDV (SEQ ID NO: 2159)
I031G05	1275	147 - 259	170 - 183	199 - 205	238 - 248	1 - 131	26 - 35	50 - 66	99 - 120	GREDTDKVKPWDRYYHYYYMDV (SEQ ID NO: 2809)
I031G06	1276	147 - 258	170 - 182	198 - 204	237 - 247	1 - 131	26 - 35	50 - 66	99 - 120	GREDTDKVKPWDRYYHYYYMDV (SEQ ID NO: 2809)
I031G07	1277	147 - 259	171 - 183	199 - 205	238 - 248	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWYDALTGDSSYHSAMGV (SEQ ID NO: 2816)
I031G09	1278	147 - 263	170 - 183	199 - 209	244 - 252	1 - 131	26 - 35	50 - 66	99 - 120	GREDTDKVKPWDRYYHYYYMDV (SEQ ID NO: 2809)
I031G12	1279	145 - 256	168 - 180	196 - 202	235 - 245	1 - 129	26 - 35	50 - 66	99 - 118	AATTSQKHNKYAYYFYGMDV (SEQ ID NO: 2131)
I031H01	1280	137 - 250	160 - 173	189 - 195	228 - 239	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
I031H02	1281	142 - 255	165 - 178	194 - 200	233 - 244	1 - 126	26 - 35	50 - 66	99 - 115	AKGYYYDSSGASDVFDV (SEQ ID NO: 2871)
I031H03	1282	147 - 260	170 - 183	199 - 205	238 - 249	1 - 131	26 - 35	50 - 66	99 - 120	GREDTDKVKPWDRYYHYYYMDV (SEQ ID NO: 2809)
I031H06	1283	144 - 257	167 - 179	195 - 201	234 - 246	1 - 128	26 - 35	50 - 66	99 - 117	DKAHGEYGRDYYYYYGMDV (SEQ ID NO: 2735)
I031H09	1284	144 - 255	167 - 179	195 - 201	234 - 244	1 - 128	26 - 35	50 - 66	99 - 117	DKAHGEYGRDYYYYYGMDV (SEQ ID NO: 2735)
I031H10	1285	143 - 256	166 - 179	195 - 201	234 - 245	1 - 127	26 - 35	50 - 66	99 - 116	DRGYTGYDRLVGGYYFDF (SEQ ID NO: 2931)
I031H11	1286	135 - 246	158 - 170	186 - 192	225 - 235	1 - 119	26 - 35	50 - 66	99 - 108	DTVRSGGMDV (SEQ ID NO: 2804)
I033A08	1287	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 37	52 - 69	102 - 117	DRYDILTGYYYYGMDV (SEQ ID NO: 2129)
I033B11	1288	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 37	52 - 69	102 - 117	DRYDILTGYYYYGMDV (SEQ ID NO: 2129)
I033C01	1289	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	EVRNYDLLTRSYLAGPLDN (SEQ ID NO: 2751)
I033C08	1290	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	EMGYDILTGYYLNYMDV (SEQ ID NO: 2862)
I033D02	1291	138 - 245	161 - 171	187 - 193	226 - 234	1 - 122	26 - 35	50 - 66	99 - 111	GDYDILTGYYMDV (SEQ ID NO: 2781)
I033D03	1292	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I033D05	1293	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I033D11	1294	140 - 247	161 - 171	187 - 193	226 - 236	1 - 124	26 - 35	50 - 66	99 - 113	VKRDILTGYVEGMDV (SEQ ID NO: 2869)
I033D12	1295	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	GGPHYDILTGYYMAVGFDI (SEQ ID NO: 2962)
I033E01	1296	139 - 249	161 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	DIDARLAALDAFDI (SEQ ID NO: 2794)
I033E06	1297	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATHDPLTGYSFDGFDI (SEQ ID NO: 2780)
I033E11	1298	143 - 253	165 - 177	193 - 199	232 - 242	1 - 127	26 - 35	50 - 66	99 - 116	HRSRSCSSTSCRNDAFDI (SEQ ID NO: 2770)
I033E12	1299	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	EMGYDILTGYYLNYMDV (SEQ ID NO: 2862)
I033F03	1300	139 - 246	160 - 170	186 - 192	225 - 235	1 - 123	26 - 35	50 - 66	99 - 112	EGAADYLNGQYFQD (SEQ ID NO: 2768)
I033F08	1301	145 - 256	167 - 179	195 - 201	234 - 245	1 - 129	26 - 35	50 - 66	99 - 118	QKVYYDILTGYNYYYYGMDV (SEQ ID NO: 2767)
I033F10	1302	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	EVRNYDLLTRSYLAGPLDN (SEQ ID NO: 2751)
I033F12	1303	134 - 241	155 - 165	181 - 187	220 - 230	1 - 118	26 - 35	50 - 66	99 - 107	DIDIGGDDS (SEQ ID NO: 2954)
I033G01	1304	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGGNYDILTGYYIGNGAFDI (SEQ ID NO: 2158)
I033G03	1305	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	PQGVTLVRGAETDAFAI (SEQ ID NO: 2925)

I033G08	1306	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I033H04	1307	140 - 247	161 - 171	187 - 193	226 - 236	1 - 124	25 - 34	49 - 65	98 - 113	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I037A05	1308	139 - 246	160 - 170	186 - 192	225 - 235	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYGMDV (SEQ ID NO: 2133)
I037B03	1309	141 - 251	163 - 175	191 - 197	230 - 240	1 - 125	26 - 35	50 - 66	99 - 114	SHYDILTRLNYWYFDL (SEQ ID NO: 2950)
I037B04	1310	144 - 251	167 - 177	193 - 199	232 - 240	1 - 128	26 - 35	50 - 66	99 - 117	DPGYYDILTGYFHRYGMDV (SEQ ID NO: 2922)
I037C04	1311	142 - 252	164 - 177	193 - 199	232 - 241	1 - 126	26 - 35	50 - 65	98 - 115	ENGDYDILTGQTFYGMDV (SEQ ID NO: 2752)
I037C06	1312	141 - 249	163 - 173	189 - 195	228 - 238	1 - 125	26 - 35	50 - 66	99 - 114	LYYDILTGYHWDAFDI (SEQ ID NO: 2882)
I037C08	1313	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 66	99 - 113	DGIDILLVPAALMDV (SEQ ID NO: 2160)
I037D11	1314	136 - 246	158 - 171	187 - 193	226 - 235	1 - 120	26 - 35	50 - 66	99 - 109	SQWLEHDVFDI (SEQ ID NO: 2864)
I037E06	1315	144 - 251	165 - 175	191 - 197	230 - 240	1 - 128	26 - 35	50 - 66	99 - 117	DRRDYDLLTRYYYYYGMDV (SEQ ID NO: 2928)
I037F04	1316	144 - 251	165 - 175	191 - 197	230 - 240	1 - 128	26 - 35	50 - 65	98 - 117	KQRGDYDILTGYQLGYAFDI (SEQ ID NO: 2808)
I037G01	1317	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	SHYDILTRLNYWYFDL (SEQ ID NO: 2950)
I037G03	1318	146 - 256	168 - 181	197 - 203	236 - 245	1 - 130	26 - 35	50 - 66	99 - 119	DLGSFYDILTALRLENYGMDV (SEQ ID NO: 2963)
I037G10	1319	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 66	99 - 113	DYYDILTKLPYGMDV (SEQ ID NO: 2975)
I042A07	1320	144 - 251	167 - 177	193 - 199	232 - 240	1 - 128	26 - 35	50 - 66	99 - 117	VSPSYDILTGYYLPHAFDV (SEQ ID NO: 2849)
I042A10	1321	142 - 249	165 - 175	191 - 197	230 - 238	1 - 126	26 - 35	50 - 65	98 - 115	GPRYYDILTGYRYNWFDP (SEQ ID NO: 2801)
I042B03	1322	140 - 247	161 - 171	187 - 193	226 - 236	1 - 124	26 - 35	50 - 66	99 - 113	DIDDILTGYVLGMDV (SEQ ID NO: 2924)
I042B12	1323	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	SHYDILTGLNYWYFDL (SEQ ID NO: 2166)
I042D01	1324	136 - 246	158 - 171	187 - 193	226 - 235	1 - 120	26 - 35	50 - 66	99 - 109	QQWLPYDAFDI (SEQ ID NO: 2839)
I042D03	1325	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 68	101 - 113	AYYDILTGYFFDI (SEQ ID NO: 2873)
I042D10	1326	142 - 252	164 - 177	193 - 199	232 - 241	1 - 126	26 - 35	50 - 65	98 - 115	ERADYDILTGYYFYGMDV (SEQ ID NO: 2802)
I042E10	1327	147 - 257	169 - 182	198 - 204	237 - 246	1 - 131	26 - 37	52 - 69	102 - 120	ERPYYDILTGYTVTYGMDV (SEQ ID NO: 2798)
I042E11	1328	140 - 247	161 - 171	187 - 193	226 - 236	1 - 124	26 - 35	50 - 66	99 - 113	DEYDILTGLLQGMDV (SEQ ID NO: 2883)
I042F08	1329	142 - 252	164 - 177	193 - 199	232 - 241	1 - 126	26 - 37	52 - 67	100 - 115	GDYDILTGYPLHAFDI (SEQ ID NO: 2738)
I042F12	1330	140 - 247	161 - 171	187 - 193	226 - 236	1 - 124	26 - 35	50 - 66	99 - 113	DGYDILTGYYFGMDV (SEQ ID NO: 2976)
I042G08	1331	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	EHYDILTGYSLLGMDV (SEQ ID NO: 2907)
I042G10	1332	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	SHYDILTGLNYWYFDL (SEQ ID NO: 2166)
I042H03	1333	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 65	98 - 116	GSLYYDILTGYYIGNAFDI (SEQ ID NO: 2759)
I043A03	1334	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	DGYYDILTGGFYYYYGMDV (SEQ ID NO: 2899)
I043B02	1335	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 65	98 - 115	GGYYDILTGYLVYYGMDV (SEQ ID NO: 2744)
I043B03	1336	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I043B06	1337	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 66	99 - 116	DQQYDILTGYHIDYYMDV (SEQ ID NO: 2828)
I043B07	1338	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDGFDI (SEQ ID NO: 2153)
I043B09	1339	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 65	98 - 116	HVRDYDILTGYYRGHHFDY (SEQ ID NO: 2727)
I043D11	1340	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	EVRNYDLLTRSYLAGPLDN (SEQ ID NO: 2751)
I043E05	1341	143 - 250	164 - 174	190 - 196	229 - 239	1 - 127	26 - 35	50 - 66	99 - 116	TESNYDILTGYYWPSMDV (SEQ ID NO: 2940)